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Original Contributions

Amebiasis

J. ARNOLD BARGEN, M.D.
Rochester, Minnesota

THE experience of physicians who have dealt with intestinal problems during the last thirty years suggests that amebiasis has been the first diagnosis in many cases of intestinal conditions in which diarrhea is a prominent symptom. No one should underestimate the importance of accurate diagnosis and adequate care of the patient who has a bona fide infection with Entamoeba histolytica, but it has been rather easy, in considering a patient who had diarrhea, to think of amebiasis, give the patient some antiamebic therapy, and then, if improvement did not come, go more thoroughly into the examination to reach a more definitive diagnosis. This approach to the problem has been rather too prevalent and it should be decried. Every effort should be made in any given case of diarrhea to make an accurate diagnosis before undertaking therapy, because there are so many different types of intestinal disorders associated with this symptom and the treatment varies with the nature of the condition.

Surveys by physicians in different parts of the country indicate that amebiasis occurs in 5 to 10 per cent of the people of the United States. Some have suggested an incidence of 20 per cent but this is probably far too high. At one time amebiasis was considered a disease of the tropics or at least a disease of warm climates where sanitation was not satisfactory. However, the disease has been found universal in its distribution over the globe. This has been known for many years by physicians everywhere, and no longer is it thought that amebiasis occurs much more frequently in southern regions of the United States than it does in Minnesota. Consciousness of its presence in the people who pass through the office of the everyday practitioner of medicine is the factor of greatest importance toward its recognition. Control of water supplies, proper food handling, and elimination of insects that are transmitters of the causative agent constitute important steps in the eradication of this serious disease. Too frequently the corner grocery store may be the distributor of amebae. With our modern methods of transportation, fresh vegetables can be shipped almost everywhere at all times of the year. It is important then that we make sure of the way these vegetables were fertilized and that they be carefully washed before eating.

Serious as amebiasis may be, it is nevertheless unfortunate when a patient who does not have amebiasis is treated for it on a trial basis. For instance, if a patient who has ulcerative colitis is given an unusual amount of arsenic in the form of carbarsone or treparsol as a result of an erroneous diagnosis of amebiasis, he may fail to respond later to other more satisfactory measures of therapy. How serious amebiasis or amebic dysentery can be will be illustrated by a case which I shall report later.

Of much greater importance, however, is the case in which the patient is found to be infected with E. histolytica and takes some form of treatment, which eradicates enough of the amebae so that none are found in the stools, only to have the symptoms recur in a few months. Equally important is the case in which there is complete eradication of the amebae, and then the patient goes back to living in the same environment in which he lived before, only to become reinfected. Adequate methods of therapy are available for amebiasis, and complete relief from it is not difficult. The important problem is that of reinfec-

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tion. This is particularly so among our neighbors across the border. At the Mayo Clinic we see many patients from the southern part of our hemisphere, many of whom carry E. histolytica without the amebae causing any symptoms. These patients apparently have become immune to the action of this parasite, and so the parasite lives in happy commensalism with his host. However, such a person may leave the parasite in Minnesota or California or Florida, and someone not adjusted to its activities may become infected and suffer a violent illness.

Cases of amebiasis occurring in this manner, as a fulminating or acute illness, are relatively uncommon but they are of sufficient importance and frequency that the practitioner of medicine should be constantly on the lookout for them.

The chronic form of amebiasis is of much greater importance than the acute form. It causes ill health, lowered vitality and decreased resistance to other infections. Chronic amebiasis seldom impels a patient suffering from it to visit his physician; and thus, perhaps, the physician does not have in mind the possible presence of the disease. However, these patients can and do transmit the disease. The infection is frequently water-borne and is due to poor sanitation, but it is also commonly transmitted by food, food handlers and insects.

During the surveys in various parts of the country, members of the personnel of hospitals have been found to be infected with amebae. This is a not unusual occurrence, and it brings home the point that persons working in hospitals, in and around the kitchen in particular, should be carefully examined to be sure that they do not carry any transmissible disease.

Incidence

Someone has observed that amebiasis exists where people exist, and this is probably a reasonably true statement. Craig and Faust[1] have estimated that 20 per cent of the people of the United States have amebiasis; that would mean more than 30,000,000 persons. As a matter of fact, only about 5,000 cases a year are reported. However, the true prevalence of amebiasis, as opposed to the reported prevalence, may reach figures as high as 80 or 90 per cent in some regions. Although amebiasis is commoner and more severe in tropical and subtropical regions than in temperate regions, its frequency is less dependent on geographical distribution than on the level of sanitation in a given locality. Epidemics of amebiasis are unusual, but they can occur as a result of gross contamination; witness the epidemic in Chicago in 1933. Frazier,[2] working in an institution in Ohio in which the population is 3,000 persons of retarded mental development, found 800 cases of infection by E. histolytica but made the diagnosis 2,000 times; in other words, there probably were infection and reinfection.

The importance of the problem of sanitation and cleanliness in regard to infestation by amebae is well illustrated by the following facts: Many authorities had predicted a great increase in amebiasis after World War II, in which our boys fought in the Pacific. However, McHardy[3] has called attention to the fact that this anticipated increase has not materialized. This is as one would expect, for in the United States, where sanitation facilities are at their best, reinfection by amebae should not take place and once the amebae are eradicated, the former hosts should not have the parasite again. Unfortunately, this is not always the case. McHardy has estimated the incidence in the United States as about 3.9 per cent, gathering his data from reports of members of the American Gastroenterological Association, from the departments of parasitology of various medical schools and from other sources.

Diagnostic Considerations

It must always be remembered that amebiasis is transmitted from hand to mouth. Persons with unclean habits should not touch food which others are to eat. Human manure should never be used for the fertilization of vegetables; however, it is still being used in some places. In this way, improperly prepared vegetables may transmit the trophozoites and cysts.

The trophozoites may be destroyed by the gastric secretions, but from an epidemiologic standpoint the cysts of E. histolytica are much more important than the trophozoites. It has been found that a patient who has acute symptoms may pass an average of 15,000,000 cysts daily, and these cysts may remain viable for days. An "ameba carrier" is in reality a person who has amebiasis that has not manifested severe enough symptoms to necessitate the attendance of a physician. The seriousness of an epidemic of amebiasis

is comparable to that of an outbreak of smallpox, yellow fever, bubonic plague or other similar acute conditions. However, although epidemics of the diseases just mentioned usually create a panic and result in prompt and drastic measures to clear up the infection, an epidemic of amebiasis frequently may be dealt with rather lightly and allowed to have its own way.

Most persons who are hosts to E. histolytica seem to have some symptoms that may be ascribed to its presence. Much has been said about the "carrier state" of amebiasis, but recent studies by physicians from various parts of the world indicate that this term has been used too freely, with the resulting tendency not to take the presence of E. histolytica in carriers seriously enough. Albright and Gordon[4] stated that there is no such thing as a healthy carrier of amebiasis. In an editorial published in 1947[5] it was stated, "The carrier represents an active stage of the disease." The evidence concerning the inability of the parasites to live in the lumen of the bowel without producing lesions is rather conclusive. The aim of specific treatment is the eradication of all the parasites from the host.

Diagnosis

Frazier has suggested classification of persons infected with amebae into five categories: (1) the group in which the host is entirely asymptomatic and simply a carrier of E. histolytica; (2) the group in which symptoms are local or systemic without diarrhea but in which gaseous dyspepsia, anorexia, fatigability and other symptoms are prominent and the patient has amebae in the stools; (3) the same as group 2 except that the patients also have periodic diarrhea; (4) the group with classic amebic dysentery; (5) the group with complications. From the standpoint of diagnosis, such a classification may be helpful, but from a standpoint of treatment, not so much can be said, because symptomatic or not, all persons infected with E. histolytica should be treated.

General physical examination may not reveal anything of significance. Certain complications, however, such as hepatic abscess or pulmonary infection, may direct attention to the source of the trouble. Digital investigation of the rectum usually does not offer diagnostic data except when the disease is advanced, and then the ulcers cannot be distinguished from those of tuberculosis. The stiff, diffusely narrowed, tubelike rectum characteristic of thrombo-ulcerative colitis is not found in cases of amebiasis. Moreover, the rectal wall tends to be soft and pliable, like that of the normal rectum.

The absolute diagnosis of amebiasis is dependent on the finding of E. histolytica in the feces or other bodily discharges. It is important to adopt a standard procedure for preparing the patient for these examinations. It is best to collect the specimen near the laboratory, and it is well to have toilet facilities at hand.

The patient should be advised to have a free bowel movement about twelve hours preceding collection of the stool to be examined, and if he does not have diarrhea he is directed to take from ½ to 1 ounce (about 15 to 30 gm.) of magnesium sulfate on the morning of the examination and then to eat his usual breakfast.

Oily preparations and oily food should be avoided for at least forty-eight hours before the patient takes the salts. It is well to have the entire stool for examination; if it is formed, material should be taken from several places; if it contains patches of blood, pus or mucus, samples of these should be examined. Material from several portions of loose stools also should be selected.

The typical stool when the disease is acute is often reddish brown, and it may contain dark-brown streaks of mucus. Here and there will be flecks of bloody mucus. Charcot-Leyden crystals are frequently present. The stools of patients who have amebiasis do not contain the quantities of pus seen in the stools of those who have thrombo-ulcerative colitis. Although they may contain more blood than pus, rarely are the massive bloody discharges that are encountered in severe thrombo-ulcerative colitis seen in amebiasis.

The stools should be examined immediately, or at least within thirty minutes after passage, for motile vegetative forms of the ameba and also for cysts. Preparations for microscopic examination may be made by emulsifying a small portion of the stool in a drop of isotonic saline solution placed on a clean glass slide, or a weak solution (1:1,000) of water-soluble eosin may be used instead of saline solution. A coverglass is placed over the material on the slide to be examined. The emulsion should be homogeneous and thin. Strong solution of iodine U. S. P. (Lugol's solution), run under the coverglass or used to emulsify the feces, is helpful. It will aid in the observa-

tion of the nucleus of the motile ameba, in counting nuclei in cysts and in identifying the masses of glycogen.

The examination should be made in a warm room, and a desk light shining on the stage of the microscope may be used. The amebae are refractive, and the light entering the field should be such as to allow them to stand out sharply.

It is a good plan, if amebiasis is strongly suspected and amebae are not found on the first and second examinations, to examine at least three loose stools on as many consecutive days. The formed stool can be emulsified with isotonic sodium chloride solution and centrifuged at a moderate rate, and the sediment can then be examined to advantage.

Other methods of examination of stools, such as by permanently stained preparations and cultures, are technically cumbersome and not in general use, although they give good results in the hands of expert parasitologists.

Complement-fixation tests have come into use in some large laboratories. Until recently, they have been more experimental and confirmatory than of real practical value to the average physician. In 1948[6] it was stated that the complement-fixation test was still considered unreliable, that the incidence of errors was still too great and that it was not a substitute for examination of the stool.

It is generally agreed now that the complement-fixation test as performed at the National Institutes of Health, the Army Medical Center or the Communicable Disease Center almost always gives positive results in the presence of amebic hepatitis or amebic abscess of the liver and is a useful adjunct in the diagnosis of these extracolonic lesions.

Proctoscopic examination is a valuable aid to diagnosis. About a third of the patients who have active amebic dysentery have demonstrable amebic proctitis, but only slightly more than a tenth of the patients who are infected with E. histolytica have grossly visible ulcers in the rectum. The proctoscopic appearance of the rectal lesions, even when repeated examinations of the stools give negative results, often provides sufficient evidence for a positive diagnosis. Even when E. histolytica cannot be demonstrated in the stool, it may be found in great numbers in the scrapings taken from the bases of the ulcers.

In the general run of cases, the ulcers are discrete and the mucosa between them, although not normal, is so mildly inflamed as to seem relatively uninvolved. In many cases of severe diarrhea resulting from E. histolytica, the rectal and sigmoidal mucosa appears normal or only slightly hyperemic on proctoscopic examination. However, when the ulcers appear, they are typically discrete and do not have any characteristics that might lead to confusion with any other type of rectal ulcer, except certain types of tuberculous ulcers and, occasionally, those associated with the presence of Balantidium coli. The ulcers of amebic dysentery, even in its earliest stage, are not very large or very numerous; the large ulcers, which, it is believed, result from secondary infection, are not to be considered as a part of the characteristic picture.

The amebic ulcer usually appears on the prominent folds of the intestinal wall or involves the valves of Houston. The margins are undermined by infiltration of the ulcerative process, and prominence of the ulcer is increased further by accumulation of material on the base, composed largely of numbers of E. histolytica. This accumulation projects above the margin of the ulcer; it presents a grayish-white covering over the center of the ulcer. This grayish-white cap is easily swabbed away, after which the true base of the ulcer is revealed right below the surface of the overhanging margins. This is the explanation of the punched-out or umbilicated appearance of the amebic ulcer. An amebic ulcer may be as small as 2 to 3 mm. in diameter, or it may be large and sloughing and measure 2 to 3 cm. in diameter, or even more, with irregular margins and overhanging, ragged edges; the latter type usually is seen fairly high in the colon. The usual ulcer is about 3 to 8 mm. in diameter, and there is generally a small zone of hyperemia surrounding it. In cases of acute amebiasis, in which the patient suffers from severe prostration and passes an excessive number of stools and in which sloughing and bleeding are present, it is difficult to identify any ulcer; the involvement is massive and diffuse, and a single ulcer is seen only occasionally in the sloughing, bleeding mucosa.

Roentgenologic examinations, after a barium sulfate enema, of patients who have amebiasis are important. Usually results are negative, and the examination thus helps rule out other intestinal lesions. In experience at the Mayo Clinic, patients

who present positive roentgenologic evidence of amebic colitis are rare; when such signs are present, they are usually in the cecum and ascending colon. The positive evidence of amebiasis obtained on roentgenologic examination of the colon usually consists of a deformity that, in general, resembles that of other chronic ulcerative diseases. The differential diagnosis is based principally on the distribution of the involved segments. Thus, in the roentgenologic examinations of some patients, extensive involvement by destructive disease is noted in the cecum, the ascending colon and the rectum. The rest of the colon may be roentgenologically normal. In the North Temperate Zone, ulceration of the colon of amebic origin is likely to be less severe and less extensive than that which is of tuberculous or streptococcic origin. In a few instances, however, a deformity involving most or all of the large intestine has been observed, which under treatment has disappeared almost entirely. When the deformity has been extensive, the regular, smooth, narrowed colon characteristic of chronic ulcerative colitis is not present, but, rather an irregular deformity is shown. The impression given, even in extensive disease, is that involvement is more mucosal than mural.

Complications

It must always be kept in mind that the presence of E. histolytica in the intestine may be associated with distant metastatic lesions or abscesses of various kinds. These include particularly abscesses of the liver, lungs and brain, but pericarditis, pleuritis, splenic and urogenital abscesses and cutaneous ulcers have also been found. In addition to the abscesses of the liver, which are usually single and are situated in the right lobe, a condition described as "amebic hepatitis" is recognized. Thus, not infrequently, a systemic disorder may call attention to the presence of amebae in the intestine. Occasionally, the only evidence of systemic disease is an unexplained fever, which may go unrecognized for a long time until someone examines the stools of the person with the fever.

Amebic granulomas have occasionally been mistaken for carcinoma of the rectum. A cursory examination with the finger and even by proctoscopy has made it impossible to differentiate these conditions in an occasional case. Whenever there is any doubt, material for examination for parasites should be taken. Much commoner than this, however, is amebic hepatitis or local amebic abscess. The latter usually occurs in the right lobe of the liver. How serious the condition can become is illustrated by the following case:

> A man, aged forty years, working for a meat-packing company in Minnesota, who had been a serviceman in the Pacific in World War II, had had periodic diarrhea for quite a long time. However, he did not wish to report the condition to his superiors because he was allowed time off only for brucellosis and a few other infections and not for diarrhea. So he went on. However, following his death his co-workers complained that he frequently, when they were cutting a carcass, had to run for the toilet and did this fifteen to twenty times a day, so that his work was quite inefficient. He was brought to the clinic in extremis, with marked emaciation, exhaustion and shock, and died within twelve hours. Necropsy revealed a huge hepatic abscess, this time in the left lobe of the liver, perforation into the pericardium, and pericarditis, perforation into the left pleural cavity and amebae in all the fluids.

How easy it would have been to prevent this patient's death if he had reported his condition in time! This is only one illustration of failure of individuals to recognize the serious warnings and signs of an impending severe amebic condition.

Treatment

The difficulties in the problem of treatment have been largely referable to and caused by failures in diagnosis. A well-established program of therapy scrupulously followed, with avoidance of reinfection, will control nearly all cases of amebiasis. Because diagnosis has presented difficulties and many cases have gone undiagnosed for a long time, many investigators have tried new forms of therapy, always thinking that some new and better form of treatment will surpass those used before.

The efforts of therapy divide themselves into three main groups. All of them represent forms of chemotherapy, designed to annihilate the amebae or prevent their causing damage. The first includes some of the newer antibiotics. Among these, one can list aureomycin, terramycin, chloramphenicol, neomycin, bacitracin and fumagillin. The second group of drugs includes the various arsenicals, and the third a variety of therapeutic agents, such as PAA-701 (diallyldiethylaminomethylphenol dihydrochloride).

The antibiotics are not true amebicides, for they do not destroy amebae in vitro. The dose

of these substances is similar to that used for other conditions.

A number of physicians with considerable experience in the treatment of amebiasis have come to the conclusion that fumagillin is at the present time the most satisfactory of the antibiotics. McHardy and Frye[7] have been giving it in doses of 30 to 60 mg. daily for ten days. This would mean a dose of 10 to 20 mg. three times a day. They have come to the conclusion that combined therapy of one antibiotic with another may be more efficacious than any of the antibiotics alone. Anderson,[8] Black, Terry and Spicknall,[9] and Malewitz[10] have had similar experiences with fumagillin. Armstrong and associates[11] have found terramycin to be an excellent antibiotic in acute dysenteries, but with relapses they add other amebicides. Their report is based on the results of treatment in fifty-one cases.

The arsenicals and oxyquinoline continue in favor among those who have had considerable experience in the treatment of amebiasis. Levy and Talley[12] have advocated the use of mercaptoarsenal, 10 to 20 mg. per kilogram of body weight, a maximum of 1 gm. daily being given for five days. Tucker[13] has advocated the use of bismuth glycolylarsanilate (milibis), chloroquine phosphate (aralen phosphate), 500 mg. of the former three times a day, 125 mg. of the latter twice a day. Two such courses can be given. Sanchez Vegas[14] has also advocated the use of these two agents as the most effective amebicides. Ritchie and Yokogawa[15] treated with carbarsone and chiniofon 241 inhabitants of a single Japanese village, where it was said that 10 per cent of the people were infected with amebae. Among 106 re-examined five weeks later, there was only one recurrence, and seven months later, only four recurrences.

Other drugs, such as resotren, mentioned by Halawani, Abdallah, El Kordy and Saif,[16] and PAA-701, mantomide, mentioned by Dennis and Berberian,[17] have found favor recently.

When all this information is added up, one finds that the results do not surpass a suitable program in which carbarsone, emetine and diiodohydroxyquinoline (diodoquin) are used in proper amounts at properly spaced intervals. One of the important problems in the treatment of complications is the treatment of amebic abscess in hepatitis. Chloroquine phosphate has become one of the leading drugs in the control of this. A paper by Radke,[18] published in 1954, indicates that patients with localized abscesses frequently complain of sharply localized hepatic pain. In Radke's group of fifteen patients, twelve had this complaint. At this point the tenderness is at its maximum. There is a sharp extension to the back and at times to the clavicle. In six of Radke's cases the latter occurred. The diaphragm was elevated in ten cases. Treatment of these patients included the use of quinacrine hydrochloride (atabrine), 0.1 gm. four times a day for 30 days, combined for the first ten days with carbarsone, 0.25 gm. twice a day for small men and for women and three times a day for large men. If the liver is still enlarged or tender at the end of thirty days, give quinacrine hydrochloride until the condition is cleared up.

Chloroquine phosphate has been a most important drug in the recent therapy of these cases. Chloroquine phosphate is prescribed in tablets of 200 mg. each. A course of one such tablet three times a day for five days seems to be superior to emetine, as indicated by Bhattacharya,[19] who treated fourteen patients in this way with excellent results. Patel[20] treated eleven patients who had liver abscess, giving 0.5 gm. a day for ten or twelve days with good results.

Dwork,[21] in reviewing the problem of recent therapy on amebiasis, concluded that the drugs of choice at this time are fumagillin, terramycin, aureomycin, bismuth glycolylarsanilate (milibis), diiodohydroxyquinoline (diodoquin) and iodochlorhydroxyquin (vioform). I am sure there are many who would take exception to this list, but this is just an illustration of how various men have used various drugs in the treatment of this rather intractable condition and have advocated the use of various drugs in accordance with their personal experience. Since no one has had a very large experience with any single one, it cannot be said, "These are the drugs of choice. These should be used preferably to any others." And yet any program that includes the satisfactory and carefully planned combination of emetine, an arsenical and an iodide will probably give us as good as or better results than all the newer forms of therapy.

Many of the recent therapeutic suggestions will undoubtedly be found to have great value in the ultimate complete eradication of E. histolytica from human hosts. However, it can be said that, in the main, even today few diseases respond so well to treatment when it is properly given as

does acute amebic dysentery. However, eradication of the parasites, prevention of recurrence and combating of the numerous irregular relapses have often been difficult therapeutic problems. The purpose of treatment is threefold: (1) destruction of amebae in the tissue, (2) destruction of amebae in the lumen of the intestine and (3) healing of the ulcerative lesions.

I have assumed that spontaneous cure of amebiasis does not take place and that the portal of entry of E. histolytica is through the large intestine. For acute dysentery the following combination of drugs has proved eminently satisfactory: emetine hydrochloride, carbarsone or phenarsone sulfoxylate (aldarsone) and diiodohydroxyquinoline (diodoquin) or one of the oxyquinoline drugs with a high iodine content. The emetine hydrochloride is given hypodermically, the amount and manner of administration varying somewhat with the severity of the disease.

For severe attacks of amebic colitis, my colleagues and I give 1 grain (about 0.065 gm.) of emetine hydrochloride every twelve hours until 6 grains (about 0.4 gm.) have been given. For the moderately severe attack, 2/3 grain (about 0.043 gm.), given twice a day until 4 grains (about 0.26 gm.) have been given, suffices. It may be well to repeat such a course after an interval of a week. A warning must be expressed about the use of emetine. Effective doses are likely to prove toxic; doses a little greater than therapeutic amounts have been found to injure cardiac muscle, and the effectiveness of emetine alone against amebae is not great. However, emetine is an excellent adjunct to other drugs for the relief of acute symptoms. In the doses mentioned, and with a total amount of the drug of not more than 10 to 12 grains (about 0.65 to 0.78 gm.) administered to any one person, we have not encountered symptoms of toxicity. Emetine is less toxic for the liver than are other recommended drugs, and it gives quick symptomatic control, thus preparing the way for more curative drugs.

At the same time as the doses of emetine are begun, a 0.25-gm. capsule of carbarsone or phenarsone sulfoxylate is given three times a day until twelve capsules (3 gm.) have been given. If administration of emetine is to be started on a given day, the patient should start taking the arsenical that morning before breakfast. Thus, he will begin to take the arsenical twelve hours before taking emetine, and he will take his last dose of the arsenical twelve hours after the last dose of emetine. After administration of carbarsone is stopped, 0.25 to 0.5 gm. of diiodohydroxyquinoline is given three times a day for seven days. Then the whole course, including the emetine and the arsenical, should be repeated. Only an occasional person is sensitive to arsenicals and may have a reaction in the form of dermatitis, fever and vomiting and occasionally diarrhea; very occasionally, visual and acoustic disturbances have occurred. If any of these symptoms occur, administration of the drug should be stopped promptly and one of the oxyquinoline derivatives should be substituted. It has been our experience that satisfactory results in the treatment of amebiasis will be achieved if this routine is followed. We have come to the conclusion that persistent, adequate and properly timed administration of these drugs is the keystone of successful treatment. The proper combination of these drugs, given in rather large amounts over short periods and yet in amounts which are unlikely to produce toxic effects, has resulted in cure of most patients with amebiasis. Thus it is seen that a suitable and successful course of treatment in the average case of amebiasis covers 22 days.

It is to be hoped that the addition of such antibiotics as aureomycin and the use of chloroquine phosphate in some of the cases in which abscess of the liver is suspected may be important steps in the final control of amebiasis.

Comment

The ultimate solution of the problem of amebiasis may be distant, but Craig's[22] statement, that in order to diagnose 90 per cent of the cases a technician or physician should spend two years under competent instruction and during that time examine thirty to forty stools a day, is probably a most authoritative suggestion and advice for those who are interested in this problem. It points up the experience of so many, that the examination of the stools for E. histolytica is the job of an expert, someone who has had considerable experience in the examination of stools and in distinguishing between this parasite, other parasites and epithelial cells which resemble some of these organisms. Then, too, if the doubt remains and the patient's symptoms point to amebiasis, a therapeutic test with some of these drugs may be justifiable. *(References on Page 82)*

Hormonal Treatment of Advanced Breast Cancer

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THE subject matter of this paper concerns itself with a résumé of some clinical investigation which I have carried on in the past five years. I claim nothing new for the subject, but I believe its contents will reveal a new assessment of the value of the method and the results obtained. There is very little material in the recent literature on the subject and not much uniformity of opinion as to procedure and evaluation of results. Much needs to be done. Any form of treatment which is beneficial in the field of therapy in metastatic cancer of the breast deserves consideration.

The discovery by Beatson,[1] in 1896, that the ovary had a sustaining influence on breast cancer gave impetus to further study of this problem. He observed regression of two cases of cancer of the breast following oöphorectomy.

Lett[2] collected ninety-nine cases so treated and found marked improvement in 23 per cent and great benefit to another 15 per cent. This method of treatment fell into disfavor because of the added surgery and because of substitution of ovarian radiation, despite the fact that the latter method was slower and more uncertain in eliminating ovarian hormones.

Dr. Ira D. Nathanson[4] of Harvard University and his co-workers seem to have done the greatest amount of clinical investigation as regards the use of steroid hormones in the treatment of breast cancer.

The fact that castration alone has a beneficial effect on metastatic carcinoma of the breast and that estrogens and androgens likewise have beneficial effect seems rather paradoxical. Most authors agree, however, on the following points: In postmenopausal women, estrogens are superior to androgens in their objective favorable effect on the soft tissue manifestations of breast cancer. Contrariwise, androgens seem to yield a higher incidence of symptomatic relief with a relatively lower remission rate of the physical characteristics of the disease. The beneficial responses to androgens may occur in women of all ages but are usually more pronounced in the pre-menopausal era. As will be shown later, castration has an immediate beneficial effect on practically all cases of advanced breast cancer. In the pre-menopausal group, in fact up to the age of fifty-five, it is probably much safer to use just androgens because of the possibility of enhancing the growth of the carcinoma by treatment with estrogens. Most authors agree that after fifty to fifty-five years of age it is safe and probably best to use estrogen therapy. There is much evidence on the clinical results to show that estrogens and androgens exert their influences on breast cancer by somewhat different mechanisms. Androgens have a pronounced effect on bone metastases.

Nathanson noted that the pathological changes in the cancerous tissue after estrogen and androgen therapy resembled very much those following irradiation therapy. A gross observation of the primary tumor showed them to soften and some of the ulcerated areas to heal and the massive tumors to shrink very materially. He states that these same tissues showed microscopic changes similar to those seen after radiation therapy. He was also of the opinion that slow growing tumors seem to respond more satisfactorily to hormonal therapy. He further states that he was unable to determine from the histological studies whether the primary effect of steroids was on the cells or on the tumor bed. Tumors of low malignancy were the most responsive to various types of hormonal therapy. It is also generally agreed that hormonal therapy has both metabolic and hematological effects which are beneficial to the host.

This has been a difficult thing to explain because of the unknown methods of metabolizing steroids. Studies have been made on blood calcium and blood protein levels, on hemoglobin, red cell count readings and hematocrit readings, to-

Presented before the Minnesota Academy of Medicine, May 12, 1954.

gether with serum alkaline phosphotase tests, to learn more about steroid metabolism.

There is general agreement that the one common beneficial effect of treatment with hormones is the resulting sense of well-being. The uniformly elevated hemoglobins and rises in blood count suggest that the mechanism is either one of inhibiting the neoplastic cells in the bone marrow or it is one of stimulating the hematopoetic mechanism of the body directly. It is also known that hormones have a beneficial effect on protein metabolism in general. There is also the possibility that the major effects of estrogens are on the diseased cells directly, with secondary metabolic responses, and that the effect of androgens may be primarily metabolic in origin.

Nathanson[6] conjectures that the effect of androgens on protein formation may result from either stimulation of anabolism or the inhibition of catabolic processes and may be the deciding factor in the beneficial effect of this form of therapy. The fact that androgens are big factors in protein synthesis and osteogenesis must also be taken into consideration in interpretation of results. Tumor growth, therefore, may be handicapped by increased bone formation without direct effect on cancer cells. The mode of action therefore, of castration with use of estrogens and androgens is still very much unexplained. Nathanson states that it can be postulated under various circumstances that these three methods of treatment temporarily restore a substance that is hostile to the growth of cancer, or that these forms of therapy may help a natural defence reaction that in itself is not capable of reversing the course of the disease. In spite of the fact that there are so many unexplained answers in this method of therapy, it is encouraging to know that the tumor may be diverted from its anticipated course by essentially physiological processes stimulated by this form of therapy.

One can deduce that hormonal therapy is designed to alter the chemical environment of carcinoma cells dependent of hormones for their well-being. Sisson and Garland[7] mentioned that surgical castration or irradiation castration will bring about remission of metastatic lesions of bone and soft tissues in 20 to 25 per cent of the cases. Most authors feel that the percentage is closer to 50 per cent. Most authors agree that androgens should be used in treating patients under fifty-five years of age and estrogens used in the older group. Most people suffering from advanced breast carcinoma will respond to either androgens or estrogens and some people not doing well on one will improve on the other. Some authors alternate in the therapy, using both of these chemical drugs. Various doses have been suggested. The subcommittee of steroids and cancer therapy suggests doses of 150 mg. of testosterone weekly for a period of twelve weeks, minimal doses of estrogen to be 4 gm. and minimum length of treatment to be six months. Most authors agree that survival time of the patients treated for advanced cancer of the breast is increased after hormonal therapy. This is unproven statistically. The clinical course of the disease is more favorable.

Higgins and Dale[3] also suggests that the furtherance of this improvement, if hormonal therapy *per se* is not adequate, should be enhanced by adrenalectomy. This phase of therapy is not to be taken up at this discussion, however. Many authors feel that the use of hormone therapy should not be instituted until the patient has had failure from other methods of therapy, namely, radical surgery plus irradiation. The cases reported in this series are all cases having had surgery, some radical and some palliative plus irradiation of some form or other. The report of the council on pharmacy and chemistry in the *Journal of the American Medical Association* (June, 1951) gives the following results: The mean survival time of the patients treated with palliative irradiation was twelve months; with testosterone propionate, 7 5/10ths months; with estrogens, 7 6/10ths months to 13 3/10ths months. They conclude that some cancers are composed of cells of sufficient functional maturity that their activity and growth are retarded by removing the source of hormones supplying them. They also are of the opinion that immature cancers do not respond favorably to withdrawal of steroid hormones.

The twenty cases that I am reporting are chosen from some forty cases who had some form of hormone therapy, but only those cases which were well controlled and could be followed have been chosen. Some of them have not been under treatment long enough to warrant reporting on definite results. Therefore the twenty cases reported here are those that have been followed from one to five years and all of which have had adequate followup studies. As I stated before, these patients all had some type of operation, some

of which was radical surgery and some of which was only palliative plus irradiation. This form of therapy was followed by hormone therapy as soon as evidence of recurrence of tumor in any portion of the body was evident. Length of treatment varied from six months to four years.

At the beginning of treatment we were more conservative in the dosages of medication given because of the inadequate information on what was the optimum dosage to be used. There is still no uniform opinion as to what constitutes an adequate dose, although the consensus seems to be that the 100 mg. of testosterone twice a week for a period of four to six months should be adequate and that a varied dose of estrogens from 15 mg. a day to 40 to 50 mg. a day for a period of six months should be adequate for estrogen therapy. During the past two years we have had to modify this dosage greatly because of our clinical observations. It has been evident from observing our patients that when 200 mg. per week were adequate for some people, this dose had to be doubled and tripled for others. It has also been our observation that a patient not doing well on this specified dose may improve greatly upon doubling the amount. This has been especially well demonstrated by some of the cases which are described below.

We have not selected cases for hormone therapy. All patients with metastatic carcinoma received either testosterone propionate or stilbestrol. We have used testosterone on patients under fifty years of age. They were all cases that had had x-ray studies of their bones and chest to determine whether or not they had metastases to the chest or to the osseous tissues. Serum calciums were studied on a few of these people but not universally done because we found no cases in which there were marked alterations in serum calciums under therapy. We evaluated the results of the treatment by noting regression of soft tissue lesions, regeneration of osseous lesions, relief of pain and evidences of improvement in general well-being such as weight gain, improved appetite, improved states of blood depletion and clearing of pleural effusion. Unfortunately we have also had the experience of seeing in one or two cases no regression whatsoever of the disease or possibly augmentation of the disease. The complications of therapy have been very few. True, there has been an occasional case of hirsutism, an occasional case of acne and some disturbances of the libido. This has not been marked or disturbing. Stilbesterol has been the drug of choice for estrogen therapy. We have had no cases of increased or severe uterine bleeding in the use of estrogens. One must also be cognizant of the possibility of electrolyte disturbances in these patients under intensive therapy.

Case Reports

Case 1.—This patient, Mrs. R., presented herself with a tumor of her right breast at age of thirty-eight. The tumor was biopsied and found to be malignant, and she had a radical breast operation November 30, 1946. The carcinoma was described by the pathologist as well differentiated adenocarcinoma, grade II, with negative axillary nodes. Her progress was very uneventful until June, 1950, when she began to develop abdominal distress. Within ten days of this time she developed some abdominal ascites and small nodules in her pelvis. Dr. Lang saw her in consultation at this time. At operation on June 7, 1950, an inoperable carcinoma of the ovary was found with generalized metastases covering the entire surface of the liver and peritoneum. At this time she was given deep x-ray therapy to the four pelvic fields. She received a total of 7,800 r of deep therapy to the pelvic fields. During all this period the patient had been absolutely free of any evidence of recurrence of the breast carcinoma, except for a small lesion which developed in the left breast which was about ½ cm. in diameter and very firm and very freely movable.

Because of the increasing abdominal fluid it was necessary to do abdominal paracentesis July 10, 1950, and August 5, 1950, where 6 to 8 quarts of fluid were removed from the abdominal cavity each time. Notes on her chart repeatedly recorded a small tumor in the left breast which remained unchanged. Because of the persistent ascites, it was necessary to again repeat the course of x-ray in June, 1951, where 8,700 r of radiation were given to the four pelvic fields. The patient's condition remained good. She was able to do her housework, and carry on through all this difficulty. On June 26, 1951, x-rays of her chest revealed a slight amount of pleural effusion on the left; 100 mg. of testosterone were given twice a week intramuscularly. This was the first evidence of metastatic carcinoma on her breast. This is rather significant insofar as she had survived a carcinoma of the ovary with generalized metastases throughout her abdomen. This should be most inimical to the inhibition of growth of a breast carcinoma because of the ovarian secretions. However, the ovaries had a tremendous amount of radiation and this may have kept the secretions in abeyance.

X-rays taken July 28, 1951, showed more fluid in the left chest than on previous examination; and the ribs, the sixth and the ninth on the left, and the eighth and ninth on the right, were now invaded by carcinomas. On September 1, 1951, the left pleural effusion showed marked increase and the rib lesions remained about stationary. One month later, x-rays of the ribs showed slight amount of healing, the patient having been on testosterone therapy ever since June of this same

year, which meant that she had been on testosterone therapy for three months. At this time the fluid in the left chest remained about the same. On November 5 there appeared to be less fluid in the chest and the ribs

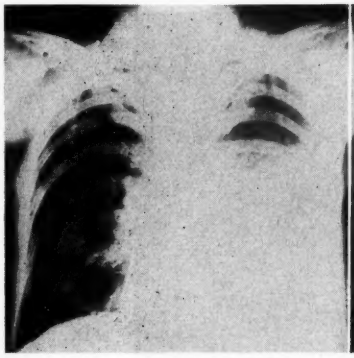


Fig. 1.

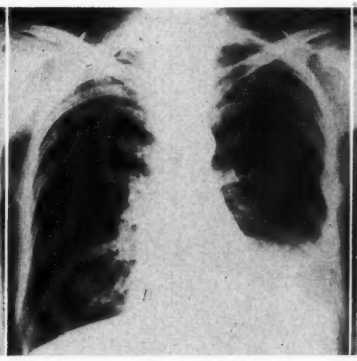


Fig. 2.

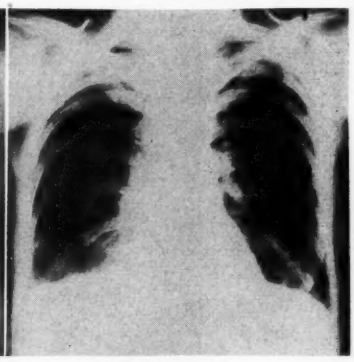


Fig. 3.

showed some evidence of healing. Further x-rays taken January 12, 1952, showed some involvement of the glenoid fossa on the left and still evidence of metastases in the various ribs described above. Although there was now a slight pleural effusion at the right base with evidence of thickening of the right pleura, there was less effusion in the left base. X-rays of February 9, 1952, showed the bony lesions were now healing and both lung bases were beginning to clear. On April 5, 1952, the pleural cavities were clear, the lung fields were clear, the pleural thickening seemed to be decreased, there was no evidence of carcinomatous metastases in the chest at this time, and the bones showed more healing. On May 31, 1952, the lung fields were clear, the bony processes were stable, and the patient was absolutely comfortable, maintaining her weight, doing all her work but having ascites.

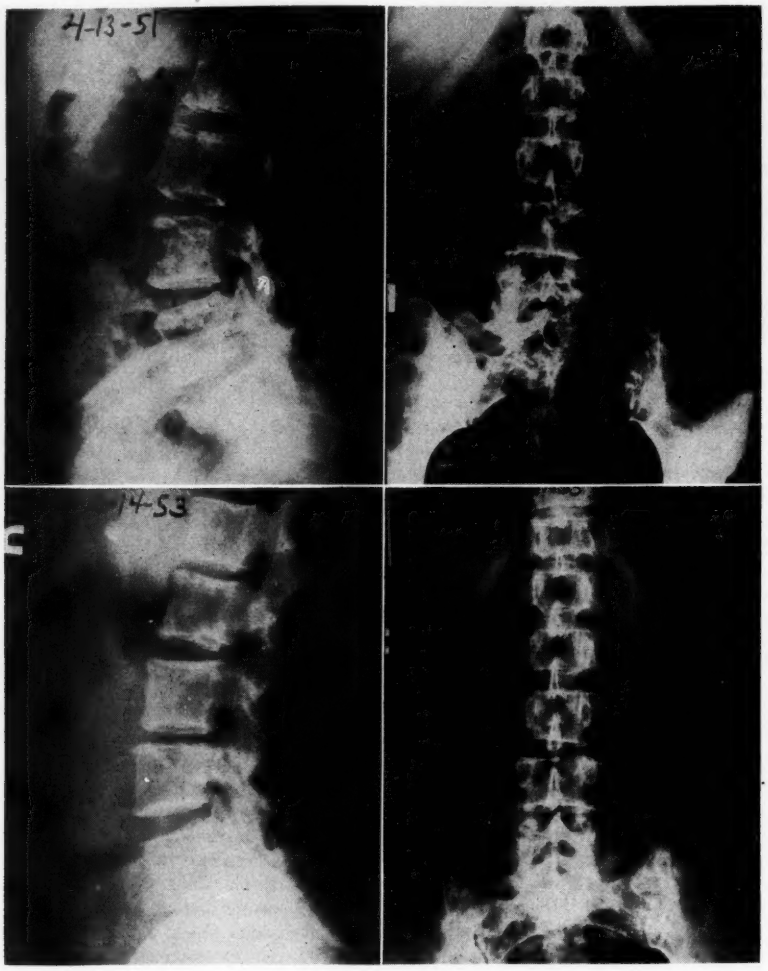
About this time the patient began rapidly accumulating ascites, but the pelvic examination revealed no increased evidence of carcinomatosis. However, in July she began to fail and the gastrointestinal studies showed that she had a high degree of intestinal obstruction at this time. This became more pronounced so that later she had to have an exploratory operation because of a complete bowel obstruction. This revealed involvement of all abdominal viscera in a carcinomatous covering which had matted all the viscera in a ball-like mass in the upper abdomen. The patient died a week later of the intestinal obstruction. It was impossible to relieve the obstruction surgically.

This case illustrates, I believe, in a classical manner the beneficial effects of androgen therapy in a relatively young woman who survived a carcinoma of the breast with surgery and no irradiation to the breast itself. She was given androgen therapy as soon as metastases developed and was able to carry on with most of her regular duties despite an intervening carcinoma of the ovary which ultimately caused her death. From November, 1946, until June, 1951, no demonstrable evidence of recurrence of breast carcinoma could be demonstrated except for the tumor of the left breast. However, she survived the breast carcinoma by approximately seven years; she survived the metastatic lesions of the breast carcinoma by thirteen months under androgen therapy, and she survived the combination of the two carcinomas, one by seven years and the other by over two years.

The evidence manifested by the films (Figs. 1, 2 and 3), I believe, speaks very strongly in favor of the fact that the only factors that sustained this woman throughout her metastases of breast carcinoma were the androgens she was taking. The fact that they show bony healing and the progressive healing of the chest lesions and the progressive disappearance of the effusion in both sides of the chest, I believe, is revealing. One can only conjecture what her expectancy might have been had she not suffered from the carcinoma of the ovary. X-rays show bony healing and regression of all chest fluid.

Case 2.—The second case that was indicative of the beneficial effect of androgen therapy was that of Mrs. H. This woman had a biopsy of a breast tumor done in Florida in 1948, when a simple mastectomy was done. In October, 1949, she presented herself with metastatic lesions in the axilla. A complete radical operation was then done, removing pectoral muscles and all the nodes in the axilla. This was diagnosed as adenocarcinoma, grade III, metastatic. This woman was put on testosterone therapy and was maintained on this therapy both by injections and by mouth in the form of linguets, a total dose of 30 mg. a day, and she was maintained in comfort on this form of therapy until April, 1951, when she developed a rather severe pain in her back and was brought to the hospital. At this time x-rays revealed that she had profound bony metastases of her ribs, spine and pelvis. The pain was so severe at this time that she was given a few x-ray treatments, simply to relieve her pain, and the doses of androgens were intensified to where she was getting 400 mg. a week for a while. This was cut down to 200 mg. a week, and she was maintained on intensive doses like this for a period of two years. In spite of the heavy doses, she had only slight voice changes and a slight amount of hirsutism but otherwise was free of symptoms. She remained well until September, 1953, when she became very ill and was hospitalized

and a diagnosis of coronary thrombosis was made. A very short time after coming in to the hospital she died. An autopsy showed no evidence of active carcinomatosis anywhere in her body. The only demonstrable cancer consisted of four or five small nodules in the liver which were umbilicated and stationary.



Figs. 4, 5, 6 and 7.

From the appearance of x-rays taken at these two-year intervals (Figs. 4, 5, 6 and 7), I believe that the amount of bony healing shown, and the fact that she was free of symptoms, maintained her body weight, maintained her blood in good condition and carried on her regular duties in life until she was struck with the coronary thrombosis, is ample proof of the efficaciousness of this form of therapy. The films show changes under hormone therapy.

Case 3.—The third illustrative case is that of Mrs. M. J., age 58, a patient seen at the clinic at the General Hospital. This patient presented herself with a cystic tumor in the left breast. She was operated upon on October 29, 1948. The first time a simple mastectomy was done; a 5 cm. cyst, nonmalignant was reported. The patient remained well until December, 1950, when she noticed induration around the scar in the region of the operation of the left breast and some enlargement of the nodes in the left supraclavicular region. She went back to the hospital where a biopsy was done, and these lesions showed a scirrhous carcinoma. A 3 by 4 cm. mass was present in the right breast, with retraction of the right nipple and an orange-peel type of skin reaction. Chest x-rays at this time were negative. Laboratory work was all normal, and the patient was well otherwise except that she showed a hypertension of 200/100.

In July, 1951, that patient was given 15 mg. of stilbesterol three times a day. This was continued for four months when it was discontinued for a short time. Dur-

ing this interval the mass in the right breast showed a very definite shrinkage and nodules disappeared promptly over the left chest wall. She was seen by Dr. Stenstrom at the University, who advised against any x-ray therapy.

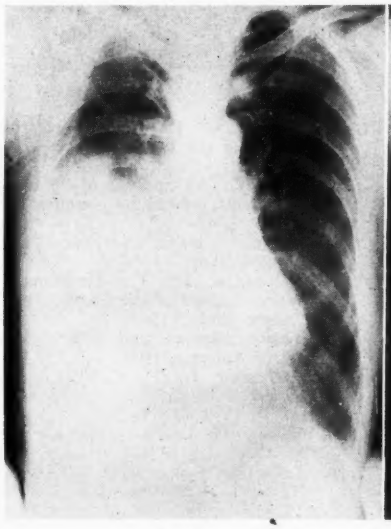


Fig. 8.

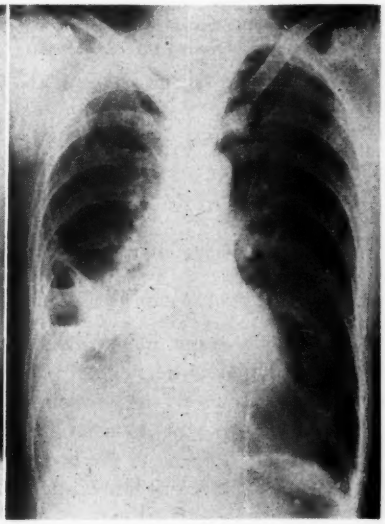


Fig. 9.

On July 30, 1951, x-rays were taken of her spine and these were normal. In August, 1951, she was again given stilbesterol, 35 mg. daily and was kept on this dosage for one month when the stilbesterol was increased to 40 mg. daily. While on the 40 mg. dosage, this patient's soft tissue lesions improved markedly. She felt well until February, 1952, and the nodule in the right breast remained smaller and stationary. Nodules began again to appear on the left chest wall. In June, 1952, it was noted that there were nodules in the right axillary space. This patient remained on 40 mg. of stilbesterol daily until November, 1952. At this time the nodules in the right breast and the right axilla were decreasing markedly in size. X-rays taken in August, 1952, showed the thoracic spine and lumbar spine to be involved with carcinomatous metastases. In January, 1953, the lungs and ribs showed questionable involvement by carcinoma. In April, 1953, there were carcinomatous nodules appearing in the lungs, ribs and the entire spine was involved. In September, 1953, x-rays showed more involvement of the ribs and across the clavicles. There was fluid in the right pleural cavity and there was further evidence of pulmonary metastases. In February, 1953, two nodules again appeared in the left chest wall. Notes made in April, 1953, showed that she was still on the same dosage of stilbesterol. The right breast and axillary nodes and skin lesions remained status quo and there were some supraclavicular nodes involved on the right. In August, 1953, this lady was put on 150 mg. of stilbesterol daily. Serum-calcium at this time was 9 mg. Serum phosphorus was 3 mg. In October, 1953, she began developing some fluid in the right chest. This was increasing slightly. Therefore the medication was changed to 200 mg. testosterone every two weeks. Serum calcium at this time had risen to 12.2 mg. On December 22 a note was made that the patient was markedly improved and generally felt better. In January, 1954, all the carcinomatous nodules were again regressing. In view of the improvement under testosterone therapy, in other words, in shifting from estrogens to androgens, it was decided to give this patient the minimum of 200 mg. a week, and she has been on this dose ever since that time and has continued to show marked improvement. The films (Figs. 8 and 9) show regression of chest fluid.

Conclusions

Any therapeutic procedure must prove its value to the patient. Uncomplicated procedures such as irradiation of ovaries plus the use of androgens and estrogens can be instituted by any physician.

I believe the evidence presented here justifies the conclusion that these measures are rational, safe, beneficial to the patient and prolong life in some cases beyond usual expectancy after generalized metastases have occurred (Table I).

These patients practically all improved subjectively though not always objectively. There is evidence here that cancer cells do not have the autonomous properties ascribed to them but are dependent on hormones for their growth.

We have positive evidence that the course of breast cancer may be retarded by the administration of sex hormones.

Further observation on the effect of hormones on breast cancer should help clarify their mode of action and help us solve the mode of cancer

TABLE I

Time elapsed from surgery to metastases: Average for group: 4 yrs. 4 mos.	Time elapsed from onset of metastases to death: Average: 19.6 mos.	
Longest interval: 9 yrs. Shortest interval: 1½ yrs.	Longest interval: 4 yrs. Shortest interval: 6 mos.	
Regression of soft tissue lesions:	Occurrence	Regression
Chest wall (local)	2	2
Lymph nodes	18	12+—
Lungs and pleura	6	3
Intracranial	1	1+—
Liver	8	2+—
Regeneration of bone	15	10+—
Evidence of subjective improvement:		
Pain relief	20	19
Weight gain	18	2
Appetite gain	18	
Blood maintenance and regeneration	15	+—

growth. A new form of therapy may provide a new approach to the study of cancer.

The response of breast cancer to hormonal therapy suggests that physiologic mechanisms for the control of cancer may be present in the body. A way of releasing this mechanism or stimulating it must be found.

There is ample evidence in the response to treatment of the cases cited above to justify the use of much larger doses of both estrogens and androgens than have previously been recommended.

Blood chemical studies and electrolyte balance must always be checked at first evidence of disturbance.

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(Continued from Page 75)

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Problems in the Clinical Diagnosis and Classification of Ventricular Hypertrophy in Adults

II. Right Ventricular Hypertrophy

BEN SOMMERS, M.D.
Saint Paul, Minnesota

THE SECOND in this series of three papers dealing with diagnostic cardiac problems is devoted to a case of isolated right ventricular hypertrophy.

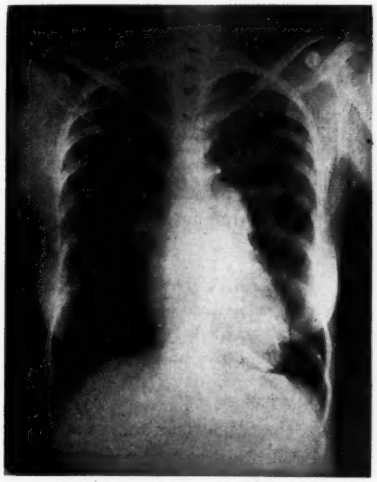

Fig. 1. Roentgenogram demonstrating right ventricular enlargement and prominence of the shadow of the pulmonary trunk.

Report of Case

A thirty-three-year-old white woman was seen in January, 1944, complaining of dyspnea and exertional pain in the thorax and arm. She had two children, aged three and one-half years, and one year. Both childbirths had been uneventful. Slight shortness of breath at night had begun when she returned home from the hospital after the birth of her younger child, and shortness of breath on exertion and angina had begun six months later. Hoarseness had been noted three months previously with a sinus infection but had persisted after the infection had disappeared. A thoracic roentgenogram taken in 1941 revealed no abnormalities, and the cardiac silhouette was normal.

Examination disclosed no cyanosis or clubbing of the fingers or toes. The only abnormalities found consisted of a soft systolic murmur along the left sternal border that was poorly transmitted and heard best in the fourth interspace, a snappy pulmonary second sound reduplicated on exercise, x-ray evidence of moderate right ventricular enlargement with a prominent shadow of the pulmonary trunk (Fig. 1) and electrocardiographic evidence of right ventricular strain (Fig. 2). The blood pressure was 108/78. The sedimentation rate was 61 mm. in one hour (Westergren). Results of the Kline test were negative.

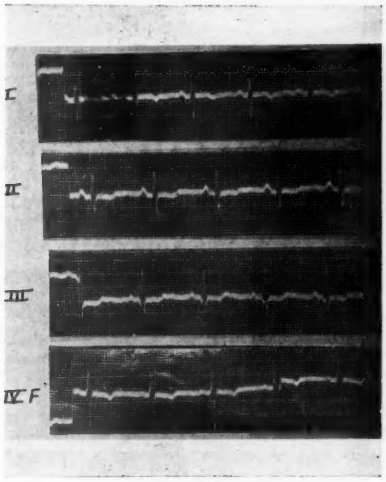

Fig. 2. Electrocardiographic evidence of right ventricular strain.

Dr. George Fahr saw this patient in February, 1944, and concurred in the diagnosis of an interventricular septal defect.

On supportive therapy, including digitalis, the patient was fairly comfortable until March, 1944, when pericarditis developed, with a septic temperature, a loud dry friction rub, thoracic pain and a sedimentation rate

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Part II of thesis submitted for admission to the Minnesota Academy of Medicine, April, 1954.

of 73 mm. She was hospitalized because of a suspicion of subacute bacterial endocarditis but repeated blood cultures remained sterile and splenomegaly and petechiae did not develop. Antibiotics were not given. At dismissal in June, 1944, the sedimentation rate was still elevated (43 mm.), but the pain and fever had abated. However, electrocardiographic studies revealed progressive right ventricular strain.

In July, 1944, a pericardial friction rub, accompanied by fever and thoracic pain, recurred for two days. In early August, progressively severe right heart failure developed, with abdominal distention, hepatomegaly and edema in the sacral region. A blood culture at this time was sterile. Death occurred in August, 1944, approximately nineteen months after onset of symptoms.

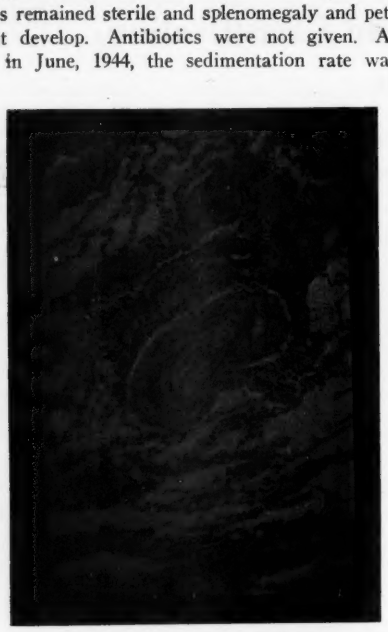

Fig. 3. Low-power magnification of section of lung, showing fibrous intimal thickening of a large muscular artery.

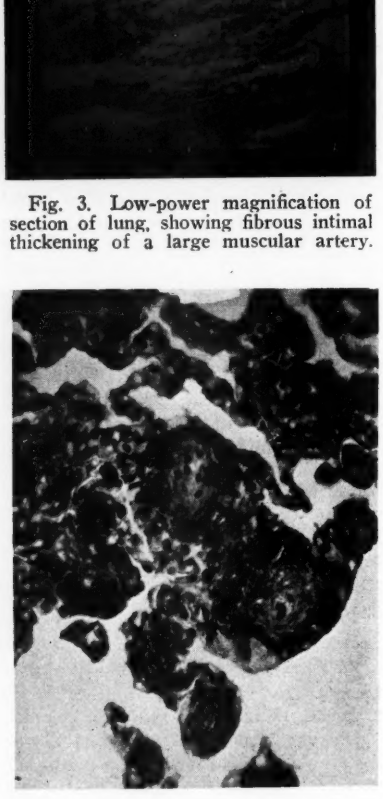

Fig. 5. High-power magnification. Fibrous intimal occlusion of small muscular arteries of lung (Verhoeff's stain).

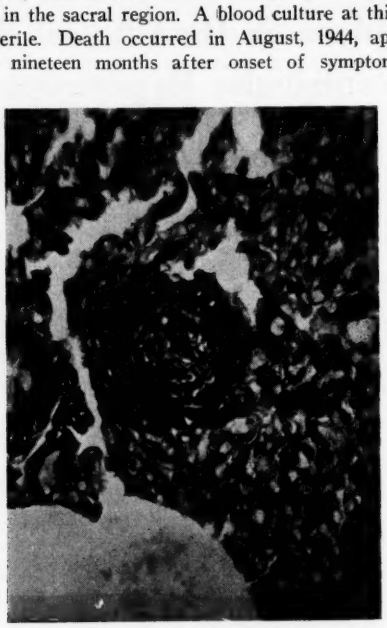

Fig. 4. High-power magnification of section of lung showing medial hypertrophy of a large muscular artery (Verhoeff's stain).

Necropsy was done by Dr. Kano Ikeda. The pericardial sac contained 60 cc. of clear, serous fluid. The heart weighed 400 gms. A few fibrous adhesions were present at the root of the pulmonary artery; otherwise the epicardium was smooth. The myocardial color was not remarkable. The left ventricle was slightly hypertrophied. The right ventricle and auricle were enormously hypertrophied and dilated. The myocardium was fairly firm. The mural endocardium was smooth, and the valves showed no disease. The root of the aorta presented a smooth intimal surface. The coronary arteries were patent and appeared normal.

Grossly, the lungs appeared normal except for slight atelectasis in the dependent portions. The bronchi, pulmonary veins and pulmonary arteries were normal. There was chronic passive congestion of the liver and kidneys.

Microscopic sections of the myocardium were not remarkable. Microscopic sections of the lungs were considered to be within normal limits at that time, showing very minimal sclerotic changes in the smaller bronchial arteries.

Comment

On restudy of this case in 1953 and 1954, these sections were sent to Dr. Jesse E. Edwards, at the Mayo Clinic, for his opinion. At his request, elastic-tissue stains were made. His report follows:

"Two processes exist. One is characterized by medial hypertrophy of the large muscular arteries; the other process consists of fibrous narrowing or occlusion of vessels in the arteriolar and small muscular arterial classes. The latter change, that is, the fibrous intimal thickening, at times has a honeycombed effect resembling organized thrombus. There is, in addition, occasional fibrous intimal thickening of the large muscular arteries. Also, there is an occasional elastic artery showing lipoid deposition in its intima associated with a fibrous proliferation, a picture to be classed as atherosclerosis."

The histologic findings are pictured in Figures 3, 4 and 5.

In 1944, cardiac catheterization had not been performed in Minnesota. The vascular changes in the lungs in this case were, however, similar to those seen in patients whose pulmonary-artery pressures have been measured and found to be elevated during life. This type of case has been called by some "primary pulmonary hypertension" and by others "pulmonary hypertension resulting from occlusion of pulmonary vessels by thrombi or emboli." Consideration of the etiology of this type of disease is beyond the scope of this paper, but the reader is referred to papers by Brenner[1] and by Dresdale and co-workers.[2] The extensive pathologic and clinical investigations of Edwards and his associates[3-11] have failed to convince him that pulmonary hypertension occurs as a primary condition.

This case, although clinically a problem as to the cause of the right ventricular hypertrophy, may now be considered an example of right ventricular hypertrophy associated with pulmonary hypertension. It is well to emphasize that, before right ventricular hypertrophy is considered idiopathic, various categories of disease known to be associated with right ventricular hypertrophy must be ruled out by necropsy. These conditions, according to Edwards,[10] include (1) impaired pulmonary venous flow, (2) disproportion between pulmonary blood flow and the capacity of the pulmonary bed and (3) common ventricular ejectile force for both the systemic and the lesser circulations in the absence of pulmonary stenosis. Edwards listed twenty-two separate conditions under these three categories, with many subdivisions. Unfortunately, many of these conditions are easily overlooked at necropsy.

Of special interest in this case was the apparent minority of pulmonary arteries involved. The small amount of tissue removed for sections may be part of the difficulty, a better method of study probably being injection of the pulmonary arteries with radiopaque material similar to the Schlesinger technique for studies of the coronary arteries.

The pathologic diagnosis of thrombotic or embolic pulmonary vascular disease in this case is well supported by the clinical history and course. Symptoms began immediately after a pregnancy and were preceded by a normal chest film two years earlier. Still unexplained, however, were the two attacks of pericarditis and their substantiation, however scanty the evidence, at necropsy.

In 1946, Castleman and Bland[12] described organized emboli of the tertiary pulmonary arteries as an unusual cause of cor pulmonale. A forty-four-year-old housewife survived for nine years with cor pulmonale after pregnancies at thirty-one, thirty-three and thirty-five years of age and a pelvic operation at twenty-nine. Pelvic thrombi during pregnancies or following the pelvic operation were believed to be the source of her emboli.

Muirhead and associates[13] reported another case following pregnancy and one associated with cryoglobulinemia. Similar cases associated with pregnancy or with transfusion of blood contaminated by cotton fibers and by other foreign bodies, and the experimental production of pulmonary sclerosis in rabbits by means of intravenously administered human fibrinous blood clots, Lycopodium spores, amniotic fluid and autogenous blood clots, attest to the interest shown in this condition of late years.

In reviewing the literature on idiopathic right ventricular hypertrophy[14-19] and earlier publications on pulmonary arteriosclerosis[20-23] one cannot help wondering whether one or more of the afore-mentioned conditions listed by Edwards was not overlooked in many of these recorded cases. The three cases of Dresdale and associates[2] classified as primary pulmonary hypertension, and encountered in a two-year period in a 500-bed general hospital were all in women who were twenty-five, thirty-five and thirty-three years of age. The second case, the only one in which necropsy was done, showed pulmonary sclerosis in both small and larger branches, with thrombi. Thrombo-embolism associated

with pregnancy might have been the causative factor in one or more of these cases, as well as in the three young women reported on by East.[14] Amniotic-fluid embolism has been reported in several cases but this substance acts as a foreign body and may be removed with passage of time, leaving thrombi in various stages of canalization.

Summary and Conclusions

A case of right ventricular hypertrophy, considered to be idiopathic after clinical and necropsy study but shown by more recent pathologic investigation to be due to thromboembolic pulmonary vascular disease associated with pregnancy, has been reported. A brief review of this subject is included, with a brief outline of the subject of primary and secondary pulmonary hypertension.

Until the numerous causes of pulmonary hypertension have been ruled out, some of which are easily overlooked, it is perhaps well to remain skeptical of the existence of primary pulmonary hypertension. Meanwhile, the antemortem diagnosis of this condition does not seem justified.

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CARDIAC OPTIMISM

Instilling a hopeful outlook is the most important thing a physician can do to assist a victim of coronary thrombosis to return to normal life. And such optimism is fully justified for most heart patients, according to Dr. Paul Douglas White of Boston, noted cardiologist recently called into consultation on President Eisenhower. Even in cases of severe heart damage requiring long convalescence, "the resumption of work is usually possible, although the occupation may need to be changed if it is too strenuous." And with the pace of present research, "there may be something just around the corner that may prove helpful to some who at present seem hopelessly ill.

"Thought of this possibility may actually aid in prolonging the life of some patients sufficiently to take advantage of new discoveries when they come," for "idleness breeds unhappiness and is actually bad for the health. It is a rare patient who is fit for nothing."—P. D. WHITE: Medigrams, *GP*, 12:89 (Dec.) 1955.

The Use of Blood and Plasma Expanders during the Third Trimester of Pregnancy

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IN the event of a major obstetric emergency, necessitating vigorous supportive therapy during the third trimester of pregnancy, the intravenous administration of a blood-volume expander, blood plasma or whole blood may be a lifesaving measure. Two examples of such emergencies are those caused by placenta previa and abruptio placentae. Both of these emergencies may result in considerable loss of blood with possibly a marked deleterious effect on the well-being of the mother, as well as the expected baby. Not infrequently, everyone practicing obstetrics may be faced with such an emergency with severe loss of blood and, at the same time, be unable to move the patient to a hospital before supportive treatment must be instituted.

The importance of whole-blood transfusion in the treatment of shock accompanying these two conditions goes without question. There is no substitute for hemoglobin and erythrocytes. The use of plasma-volume expanders is of real value at times, but it never was intended to supplant the transfusion of whole blood. However, the usefulness of plasma-volume expanders results from the low cost of manufacture, the ease of storage for long periods, and their effectiveness in emergency treatment of loss of blood volume and shock. Most of these products can be transported easily and may be administered in homes, ambulances or the emergency admitting ward of a hospital.

Of all the plasma-volume expanders currently available, dextran, polyvinylpyrrolidone and gelatin appear to meet most of the criteria required of an acceptable product. The ideal one has not been discovered.

The plasma-volume expanders appear to be of greatest use when the loss of blood does not exceed 20 per cent of the total blood volume. When more than 35 per cent of the total blood volume has been lost, the anemia commands attention. Therefore, transfusions of whole blood, with or without the use of plasma-volume expanders, are indicated.

Dextran

Solutions of dextran in this country are available under various trade names. The chemical nature and the molecular form, size and shape of the dextrans have been studied. Use of a 6 per cent solution has been effective in restoring blood volume and in improving blood pressure. Pulaski[1] stated that after injection of dextran tagged with C^{14} into the dog, the urine shows 65 to 70 per cent of the radioactivity, with 4 to 6 per cent in the expired carbon dioxide and 3 to 5 per cent in the viscera at the end of seventy-four hours. About 25 per cent cannot be found. Material marked with C^{14} also was found in the liver, spleen and lymph nodes.

Part of the retained dextran is metabolized. Michie and Ragni[2] found no clear evidence of renal damage, although depression of tubular function has been noted.

Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) is a synthetic macromolecular polymer first produced in Germany early in World War II. The raw materials used in its production are ammonia, acetylene and formaldehyde. In a concentration of 3.5 per cent in isotonic solution of sodium chloride, with a molecular weight of 40,000, this substance has a desirable colloidal osmotic pressure and viscosity. There is no evidence that this product is metabolized. Forty per cent appears in the urine in the first twenty-four hours. At the end of seventy-two hours, 28 per cent is still unaccounted for, as far as excretion in the blood or the urine is con-

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The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

cerned. In the mouse this product is stored in the endothelial cells of blood vessels, the reticuloendothelial cells, the liver and the kidney.

Gelatin

Solutions of gelatin have been used for several years. A 6 per cent solution has about the same osmotic pressure as is exerted by plasma. Particles of a molecular weight of less than 30,000 are excreted in the urine. Four hours after infusion of a 5 per cent solution of gelatin, Jacobson and Smyth[3] found that 70 per cent was still retained in the blood. Fifty per cent of the particles of a molecular weight of more than 30,000 to 35,000 are reported to be retained for twenty-four hours. This product has been used satisfactorily for treatment of patients suffering from shock. Changes in tissue produced by gelatin consist of transient swelling of the tubular epithelium of the kidney and temporary storage in the liver and reticuloendothelial system.

The use and value of whole-blood transfusion in some conditions will be referred to later in this presentation.

Emergency Measures

During the delivery of the baby, emergencies requiring supportive therapy may arise from severe bleeding, from lacerations, from postpartum atony and from retained secundines. An unusual happening, postpartum inversion of the uterus, may result in severe shock, necessitating the emergency administration of plasma-volume expanders or of whole blood.

An emergency transfusion of blood may be started with cross-matched compatible blood, using low-titer group O Rh-negative blood, if the patient is in the hospital and if his group is unknown and if sufficient time is not available for determining the group and Rh type of his blood.

In so far as possible, it is advisable to administer cross-matched blood of the same group and Rh classification as that of the patient, instead of un-cross-matched group O Rh-negative donor blood. However, if the emergency demands speedy administration of blood, low-titer group O Rh-negative donor blood may be used.

In the institution with which I am associated, blood is collected in 500-cc. vacuum bottles containing anticoagulant acid citrate dextrose solution. Disposable sets for intravenous administration are used. Fifteen-gauge or 18-gauge needles are introduced into accessible veins. Infiltration with a local anesthetic at the site of venipuncture makes the procedure more comfortable for the patient.

The rapid administration of a large quantity of whole blood sometimes is necessary. One of the commercial distributors has an administration set made of one of the plastic materials which can be used for forceful introduction of blood into the patient's veins. Another technique used not infrequently is to introduce air into the vacuum bottle and create within the bottle a positive pressure that is sufficiently high to force the donor blood into the patient's venous circulation.

It is very desirable for all physicians to be aware of the fundamental principles of this subject of emergency blood transfusion. For this procedure to be carried out satisfactorily, it is important for the physician to be able to introduce needles into veins without discomfort or trauma to the patient. Too frequently, interns, residents and others have had little or no instruction in the technique of venipuncture. It behooves all of us to teach interns and residents all the many tricks that go to make a successful venipuncture. This instruction is invaluable when emergencies arise that necessitate the intravenous introduction of fluids or whole blood for needed supportive therapy.

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Why Not Pack the Postpartum Uterus?

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THIS paper is devoted to a consideration of hemorrhage from the postpartum uterus due to atony. Bleeding due to lacerations or retained secundines are not considered, unless atony was also part of the clinical picture.

Recently, statements have been made by some rather prominent obstetricians to the effect that they did not believe in packing a postpartum uterus, or that they never had packed, or that they never would. In one instance, the obstetrician making this statement was also reporting several hysterectomies done post partum because of uterine atony.

There have been very few statements by the proponents of packing. Many good obstetricians pack the atonic, bleeding uterus. We feel that it is a good procedure. To us, it is inconceivable that hysterectomy should be done for postpartum atonic bleeding, without first having properly packed the uterus.

Some statistics are presented in Table I which support our contention that packing is a good procedure. These statistics were collected from the Edward J. Meyer Memorial Hospital and the Buffalo Hospital of Sisters of Charity, Buffalo, New York, and from the Virginia Municipal Hospital, Virginia, Minnesota. They cover all deliveries in the past six years in the first two hospitals mentioned, and all deliveries in the past twelve years in the last mentioned hospital. These are consecutive deliveries. No cases have been deleted for any reason. During the periods mentioned, there were 38,403 deliveries in these institutions; 505 cases had postpartum packing of the uterus because of atonic bleeding. There was one hysterectomy for postpartum atony. In this case, the uterus was not packed. The patient was under the care of a physician who apparently did not subscribe to the procedure of packing. There was no mortality due to postpartum atonic hemorrhage in this series. There were no serious complications in the patients who were packed. Besides the intrauterine pack, we also use the prescribed methods of uterine massage, intravenous Pitocin, ergonovine and blood transfusions. We may have employed the pack somewhat more often than absolutely necessary. Since none of these women died of postpartum hemorrhage or lost her uterus, we feel that this is not a serious fault.

TABLE I. POSTPARTUM ATONIC BLEEDING IN 38,403 DELIVERIES

Hospital	Deliveries	Packed for Bleeding	Hysterectomies-Atonic Bleeding	Mortality
Edward J. Meyer Memorial	6,309	179	0	0
Sisters of Charity	22,618	310	0	0
Virginia Municipal Hospital	9,476	16	1*	0
Total	38,403	505	1	0

*This patient was not packed, by the physician's choice. Actually, no hysterectomies were performed among those patients packed.

The physiology of postpartum uterine atony is not well understood. There are several questions which must be answered by any physiological explanations of atony. (1) Why does a uterus which has gone through a normal first, second and third stage of labor suddenly become atonic in the fourth stage? (2) Why does a uterus which has gone through an abnormal, inertia-type of first, second and third stage of labor have a normal fourth stage?

Certain terminology should be understood before considering atony. By *contraction,* we mean the act of muscle shortening. By *retraction,* we refer to the relaxation phase between contractions. During this relaxation phase, however, the muscle does not return completely to its original length. Eastman[1] states that retraction is the ability of a muscular viscus to contract down on its decreasing contents with the tension remaining constant.

Where does postpartum bleeding come from? Usually, it is from the large sinuses at the site of

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the placental implantation. How is postpartum bleeding normally controlled? Contractions of the various muscle fibers, by compressing and twisting the sinuses, staunch the flow of blood temporarily during the contraction. If retraction is adequate, even in the relaxation phase between contractions, there is enough compression and kinking of the sinuses to prevent a heavy flow. Finally, thrombosis and fibrosis control the bleeding permanently. It follows that in order to retract, the muscle must first contract. A uterus which can do neither, probably must come out. We have not seen such a uterus.

People who do not use packs have given many reasons for their ineffectiveness: packs prevent contraction; prevent retraction; cause infection; and merely soak up blood. In answer to these objections, we can state that our packs, when removed, are practically never blood-soaked; they are wet with a serous pink fluid. We have had no serious morbidity. Basic physiology teaches that increasing the tension in a hollow viscus increases the contractibility of the viscus. Reynolds, Kaiser and Harris[2] state that the contractibility and retractibility of the uterus are dependent upon the radius of curvature of each individual muscle fiber and the amount of intrauterine tension.

We believe that a uterus which is contracting and retracting enough to cause delivery of a fetus and placenta does not suddenly, totally, lose the ability to contract and retract. The delivery of fetus and placenta decreases the intrauterine tension and decreases the radii of curvature of the muscle fibers. This may remove enough of the stimulus to cause a partial loss of the contractibility and retractibility. We believe that a properly applied pack, by increasing uterine tension and the radii of curvature of the muscle fibers, increases the ability of the uterus to contract and retract, thereby controlling bleeding.

Usually, when a pack is unsuccessful, it is because it has not been properly applied. Since the gradient of contractile force is from the fundus towards the cervix, it is at the fundus that the intrauterine tension and radii of curvature must be first increased. This can be easily accomplished by one man, using a cannister-type packer* (Fig. 1) devised by one of us (E.G.W.), with a roll of sterile 4-inch gauze. The tip of the packer is inserted through the cervix to the fundus. It should be palpated through the abdomen to note that it is in correct position before packing is begun. By successive, rapid strokes of the toothed plunger, 5 to 10 yards of gauze packing can be inserted within a few seconds. Additional sterile gauze packs may be placed in the packer and tied to the preceding roll, if more packing is necessary. Increasing the gauze in the fundus backs the packer out of the uterus as it becomes full. It should be noted that no retractors are necessary and that the gauze does not touch any part of the patient before being deposited in the uterine cavity. The pack need not remain in long. Some of ours have been removed after as short a time as thirty minutes. Others have remained in twenty-four hours. Actually, as soon as the uterus begins to contract normally on the pack, it can be slowly withdrawn, removing a few feet at a time so that the uterus is not suddenly, emptied.

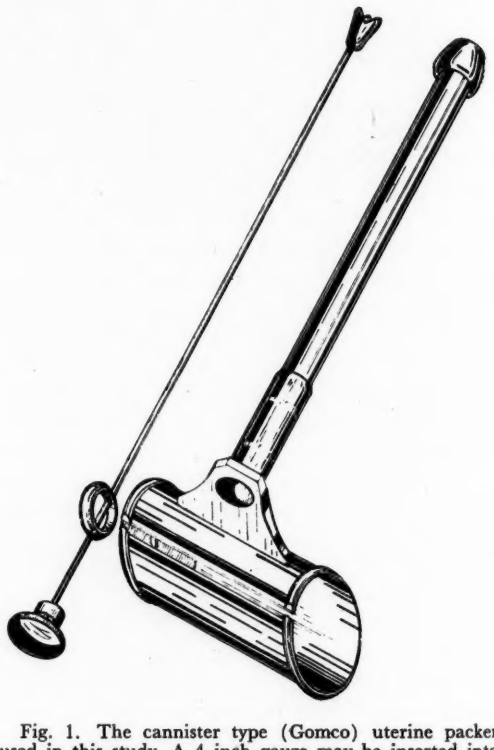

Fig. 1. The cannister type (Gomco) uterine packer used in this study. A 4 inch gauze may be inserted into the cannister and the free end brought up through the slot and into the barrel. It may be sterilized already loaded. Additional sterile 4 inch gauze rolls may be inserted as needed while the packer is in use.

*This packer is manufactured by the Gomco Surgical Equipment Corp., 828 East Ferry Street, Buffalo, N. Y.

(Continued on Page 125)

Oxygen Therapy in the Premature Infant as a Cause of Retrolental Fibroplasia

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LITTLE doubt remains that the injudicious administration of oxygen to premature infants is a major factor in the development of the retinopathy of prematurity, or retrolental fibroplasia.

This tragic disease, in which the retinal vessels and their supporting connective tissue proliferate onto the surface of the retina and into the vitreous, is the major cause of blindness in the United States today. Of all infants affected by retrolental fibroplasia, 98 per cent are premature, predominantly those whose birth weight is less than 1,500 gm. About 2 per cent of cases are found in full-term infants.

The first signs of the disease usually appear during the first month of life. The retinal vessels enlarge and become tortuous. Hemorrhage or transudation may appear and neovascularization may be present. The active stage may develop slowly or with extreme rapidity. Activity usually subsides during the third or fourth month and the cicatricial phase begins about the sixth month.

Course of Retrolental Fibroplasia

At the 1954 meeting of the American Academy of Ophthalmology and Otolaryngology, a panel on the subject of retrolental fibroplasia[1] recommended division of the course of the disease into three periods, namely active, regressive and cicatricial.

Active Period. — The panel subdivided the period of activity into the following five stages: (1) the vascular stage, in which the retinal vessels become dilated and tortuous and in which regions of neovascularization may appear in the periphery; (2) the retinal stage, in which the vitreous becomes hazy, neovascularization becomes more advanced and hemorrhage and gray edematous zones may appear in the peripheral parts of the retina; (3) the stage of early proliferation, in which newly formed vessels invade the vitreous; (4) the stage of moderate proliferation which is arbitrarily reached when such proliferation involves half the retina and (5) the stage of advanced proliferation, which is reached when the entire retina becomes detached or massive intraocular hemorrhage is present.

Regressive Period. — Regression occurs commonly. In about a third of the infants who have retrolental fibroplasia, the disease does not progress beyond the aforementioned Stage 1; the disease stops at Stage 2 in a fourth of the patients, while the disease in the remainder goes on to Stages 3, 4 or 5. When the disease is mild, the patients recover with little permanent damage. The disease occasionally may regress for a period and then briefly become active again if an infection develops.

Cicatricial Period. — The cicatricial phase follows the period of regression. The amount of permanent damage varies from none to a completely disorganized mass of detached retina, hemorrhage and proliferated vessels. The panel also divided this period into five stages as follows: (1) minor changes, consisting of a slight change in vascular caliber, small zones of retinal pigmentation or small masses of opaque tissue in the periphery of the fundus; myopia is common in these patients; (2) distortion of the optic disk, which may be caused by contraction of scar tissue in the peripheral zones; the disk and blood vessels are drawn toward a peripheral mass; (3) a retinal fold, which may extend to a mass of opaque tissue, usually in the temporal periphery, and as a rule contains the retinal vessels; several such folds may be present; (4) an incomplete retrolental mass, which may cover part of the pupillary region, and (5) a complete retrolental mass, which

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Part of a round-table discussion at the meeting of the Minnesota State Medical Association, Minneapolis, Minnesota, May 23 to 25, 1955.

From the Section of Ophthalmology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

is composed of detached retina and fibrous tissue and which may completely fill the retrolental space; elongated ciliary processes are visible at the equator of the lens; the anterior chamber may be extremely shallow but later it may become extremely deep; anterior and posterior synechiae are common; secondary glaucoma and an opaque cornea occur; because growth of the eye is inhibited, the eye remains small and the upper lids appear sunken.

The disease in about a fourth of the afflicted infants develops to Stages 4 and 5 of this cicatricial phase; in a third of the patients, it develops to Stages 1, 2 or 3, whereas the disease in the remainder heals with no visible residuals.

Pathogenesis of Retrolental Fibroplasia

Vascularization of the retinas of animals and human beings occurs relatively late in embryonal life. Vascularization in man is essentially complete at full term, whereas in mice, rats, kittens and puppies, this process continues for a variable time after birth. As a consequence, the premature infant is born with an incomplete retinal vasculature. Retinal vascular proliferation normally is most active during the sixth and seventh months of embryonal life; retrolental fibroplasia is most likely to develop in babies born at this period.

Retinal vascular proliferation progresses normally in the unborn child under conditions of low oxygen tension. If this condition persists into extra-uterine life and oxygen deficiency is absent at this time, no difficulties ensue. However, if a high oxygen tension is produced by exposure of the infant to high concentrations of oxygen, the retinal vessels constrict greatly. If this tension is maintained for three or four days, an irreversible vasoconstriction may obliterate these vessels as the result of either adhesions of the vascular endothelium or intravascular clotting, according to Ashton and associates.[2,3] Thus, hypoxia ensues and vascular proliferation begins. Instead of a smooth growth, the capillaries now sprout to form whorls of varicose capillaries like renal glomeruli. The supporting mesenchymal connective tissue also proliferates. Hemorrhage and transudation may appear, and the capillaries burst out of the retina to form sheets on the surface of the retina and in the vitreous. Retinal detachment is caused by both transudation of fluid and fibrotic strands in the vitreous.

TABLE I. INCIDENCE OF RETROLENTAL FIBROPLASIA IN PREMATURE INFANTS WEIGHING LESS THAN 1,500 GM.

Year	Infants	Retrolental Fibroplasia, Cases
1948	4	0
1949	4	0
1950	3	0
1951	14	3
1952	4	1*
1953	6	1
1954	5	1
Total	40	6

*Also one case in a 1,720-gm. infant.

Relationship to Oxygen Therapy

Typical lesions of retrolental fibroplasia have been produced by exposing newborn puppies, rats, mice and kittens to high oxygen tensions.

Szewczyk[4] presented evidence that the disease appears as a result of hypoxia induced either at or before birth, followed by further injury by means of relative hypoxia when the infant is removed too rapidly from an atmosphere containing high concentrations of oxygen.

The personnel of eighteen hospitals collaborated in a study of large groups of premature infants whose birth weights were less than 1,500 gm. This study was reported by Kinsey and Hemphill.[5] These infants at birth were assigned to one of two groups, namely (1) a "routine oxygen group" who received oxygen for twenty-eight days at a concentration of 50 per cent or more and (2) a "curtailed oxygen group" who received oxygen only on the basis of frank chemical need. The mortality rates were the same in each group. However, retrolental fibroplasia developed in 73 per cent of the first group and only 30 per cent of the second group; 25 per cent of the first group but only 6 per cent of the second group had permanent ocular damage. The initial ten days of exposure to oxygen appeared to be the most damaging. Those patients exposed to a concentration of oxygen of less than 40 per cent had a lower incidence of the disease.

During the period 1948 through 1954 at St. Marys Hospital in Rochester, Minnesota, there were 10,826 live births, of which 689 represented prematures weighing 2,500 gm. or less. Of this group, forty surviving infants weighed less than 1,500 gm. Retrolental fibroplasia developed in six (15 per cent) of this group and in one infant who weighed 1,720 gm. These babies were distributed as indicated in the table. All patients at

this hospital are under the care of Mayo Clinic physicians.

Just why cases of this disease were not encountered at the Mayo Clinic prior to 1951 is not known. Routine ophthalmoscopic examinations were not done until 1950, and consequently, undiscovered cases of subclinical disease may have occurred that regressed to Stage 1 or Stage 2 of the period of cicatrization. All three patients seen in 1951 became completely blind; they included a set of twins, as well as a child kept in oxygen for five weeks because of multiple abscesses and severe toxicity. One child with retrolental fibroplasia in 1952 was born with agenesis of the right cerebral hemisphere; the ocular disease advanced only to Stage 2 of the active period and then regressed. The other child became completely blind. The lesion in the child born in 1953 developed to Stage 5; he was born nine days before the mother died of advanced congenital cardiac disease and massive cerebral hemorrhage. The child born in 1954 sustained massive intra-ocular hemorrhage into one eye one week after birth and now has a large mass of scar tissue in the temporal portion of the fundus; the other eye has remained normal. As dilated blood vessels were not seen in either eye, the hemorrhage may not have been a manifestation of the disease but may have been due to some unknown cause.

Half of the six patients were seen in the three-year period since our "austerity" program for oxygen therapy in prematures was begun in 1952. These three infants were given a minimum of oxygen.

Management

In the management of the premature infant, it is the practice of our pediatricians to use as low a concentration of oxygen as possible during as brief a time as feasible. This is usually during the first twenty-four to forty-eight hours only. Adequate respiration usually is established during that time, and the administration of oxygen is terminated. Occasionally, use of oxygen must be resumed for short periods. The concentration is kept at a level less than 40 per cent and frequent checks on the concentration are made.

The eyes of all prematures probably should be examined by an ophthalmologist, especially if the birth weight is less than 1,500 gm. The initial examination should be made during the first week. We prefer to use 1 drop each of a 2 per cent solution of homatropine and a 10 per cent solution of phenylephrine (neosynephrine) hydrochloride for dilating the pupil. Atropine is not used in these small infants. A small lid speculum is helpful. Re-examination is done every week during the first month and every two weeks during the second and third months. If the eyes have shown no abnormalities by the end of the third month, examinations are discontinued.

If retrolental fibroplasia develops, the pupils should be kept dilated with homatropine to prevent posterior synechiae. At the present time, no therapy appears to be of avail. Transfusions have an adverse effect if the disease is present.[4] If glaucoma develops, as it does in about a fourth of the cases of severe disease, miotics such as pilocarpine or physostigmine are often effective in reducing the intra-ocular tension.

It is important to acquaint the parents of a blind child with the educational and social facilities available to such a child.

Conclusions

Retrolental fibroplasia is a disorderly proliferation of blood vessels and connective tissue induced in the undeveloped retina of the premature infant, at least in part, by injudicious use of high concentrations of oxygen.

The lowest possible concentration of oxygen administered to the premature over the shortest possible time should be the rule in management.

Great variations in the concentration of oxygen should be avoided.

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Massive Upper Gastrointestinal Bleeding

Results of Surgery during Acute Phase

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THE treatment of the patient with massive upper gastrointestinal hemorrhage has been a controversial problem for many years. There are many who believe that blood replacement and the use of a good dietary regime is the treatment of choice. This group advises operation when:

1. The patient, after being admitted in shock and given 1,000 to 1,500 cc. of blood, exhibits signs of vascular collapse.

2. The patient cannot maintain a constant blood pressure and hematocrit in spite of 500 cc. of blood every eight hours.

3. Massive hemorrhage recurs during treatment.

4. The patient is over the age of fifty and has bled to shock levels at any time, medical treatment should be used with caution.

Under such management only those patients who demonstrate persistent bleeding or recurrent bleeding are referred for surgical management of their gastrointestinal hemorrhage. With such management the mortality rate is reported in several series to be 17 to 35 per cent. Such management places the surgeon in the position of having to salvage a rather desperate situation. In spite of this adverse situation, many patients have been salvaged by surgery and at the same time have had definitive treatment for their ulcer diathesis.

Recently the surgical approach to this problem has been emphasized by several authors who point out that continued hemorrhage and repeated hemorrhage from peptic ulcer is a grave and serious problem. They also point out that surgical management of this entity can be carried out with an over-all mortality rate which is less than that for other types of management.

Inaugural Thesis presented before the Minneapolis Surgical Society, April 7, 1955.

Statement of the Problem

It was the impression of the surgical staff at the Minneapolis General Hospital that the number of patients seen at that institution with massive upper gastrointestinal hemorrhage from peptic disease was greater than usually seen at an average hospital. Ample opportunity presented itself to study this group of patients. Through the co-operation of the medical service all patients with gastrointestinal hemorrhage were admitted directly to the surgical service. During a five year period each such patient was evaluated by the surgical house staff and the attending surgical staff relative to the source of the patient's gastrointestinal hemorrhage, the amount of bleeding which had occurred and the feasibility of surgical treatment of his gastrointestinal hemorrhage. All patients were seen in consultation by members of the medical service and the patient's cardiovascular status and general physical status were completely evaluated. Surgical management of every patient with massive upper gastrointestinal hemorrhage was carried out.

Material and Methods

The material presented is taken from the surgical service at the Minneapolis General Hospital for the period January 1, 1950, to January 1, 1955, and represents 100 consecutive cases of massive upper gastrointestinal hemorrhage. The patients are divided into Series A and Series B.

Series A constitutes fifty patients who were seen from January 1, 1950, to July 1, 1951. The following criteria were used in the management and treatment of this group of patients:

1. The patient must have demonstrated gastrointestinal hemorrhage within seven days prior to admission.
2. The existence of "massive" upper gastrointestinal hemorrhage was defined by the presence of:
   (a) A hemoglobin of less than 10 grams per cent or;
   (b) A hematocrit of less than 25 volumes per cent or;
   (c) Signs of shock as manifest by a positive tilt test, a systolic blood pressure of less than 100 mm.

Hg, persistent tachycardia, peripheral vascular collapse, or;

(d) Objective evidence of massive blood loss while hospitalized.

These patients were considered to have massive gastrointestinal hemorrhage and the following principles were applied in the treatment of these patients:

1. Immediate whole blood transfusions were started and blood replacement was continued until the hemoglobin reached 14 grams per cent and the hematocrit 40 volumes per cent.

2. Concomitant medical disease must be under adequate control.

3. No bleeding diathesis should be present as ruled out by the bleeding and clotting time, prothrombin time, fractional proteins, cuff test and platelet count.

Surgical intervention was undertaken when these principles were met. The choice of procedure was left to the discretion of the operating surgeon. Deviation from these principles was permitted only when:

1. Continued bleeding as demonstrated by persistent melena or persistent hematemesis or persistent shock indicated immediate surgery in spite of an inadequate blood replacement.

2. The resumption of bleeding after all obvious bleeding had stopped indicating recurrent peptic ulceration and hemorrhage.

3. Uncontrolled medical disease.

Series B constitutes fifty patients seen between July 1, 1951, and January 1, 1955. This series differs from Series A only in that the estimation of blood loss was not done by hemoglobin, hematocrit levels or on the basis of impending shock or a positive tilt test but on the determination of plasma volume and red cell mass by the use of T-1824 vital dye. By this method adequate blood replacement could be done in relationship to quantity and to the time necessary to replace the blood loss. The definition of massive gastrointestinal hemorrhage in Series B is based upon a total circulating red cell mass deficit of more than 50 per cent. Therefore, in Series B the term "massive" gastrointestinal hemorrhage is clearly defined. When the quantity of whole blood indicated by the red cell mass deficit had been replaced, the plasma volume and red cell mass were again determined. If there had been progressive hemorrhage during the period of blood replacement, this fact was reflected at the time of the second blood volume determination and further blood was given. When a calculated normal red cell mass had been obtained, the patient was operated upon.

All of the surgical procedures were done by the surgical house staff and the attending staff of the surgical service. The results do not reflect the surgical ability of one or two surgeons but rather a group of well qualified house surgeons under the supervision of their attending staff.

No patient with esophageal varices is included in group B because other surgical principles were being applied to all patients with portal hypertension.

The surgical procedure carried out in both Series A and Series B was a subtotal gastric resection which varied in its extent from 65 per cent to 80 per cent resection. There were no vagotomies in either series.

Series A.—The average age of this group was fifty-six years. The distribution within the age group is to be found in Table I. There were no patients under the age of twenty and only one patient over the age of seventy-nine. The greatest incidence was between the age of fifty and seventy.

TABLE I. AGE DISTRIBUTION

Series A	
0-19	0
20-29	1
30-39	5
40-49	6
50-59	10
60-69	19
70-79	8
80-	1

The quantity of blood given to the patients preoperatively varied from 2,000 to 8,500 cc. The average preoperative quantity of blood was 3,500 cc.

The duration of symptoms presented by the patient varied from two hours to seven days. The average duration of symptoms prior to admission was 2.6 days. Eighteen patients (36 per cent) demonstrated melena only, fifteen patients (30 per cent) hematemesis only and seventeen patients (34 per cent) both melena and hematemesis.

The incidence of previous ulcer history was 56 per cent. No patient is included on the basis of ulcer history alone. Twelve patients gave a history of previous upper gastrointestinal bleeding;

four patients gave a history of previous perforation and twelve patients gave a history of roentgenological demonstration of peptic ulcer.

The source of the bleeding in this group of fifty patients is tabulated in Table II. The greatest incidence was due to duodenal ulcer with the second greatest incidence due to gastric ulcer. In this series there is one patient with esophageal varices and six with severe alcoholic gastritis. In one patient the source of the bleeding could not be found and an empirical gastric resection was done.

TABLE II. SOURCE OF BLEEDING
Series A

Duodenal Ulcer	30
Gastric Ulcer	12
Gastritis	6
Varices	1
Unknown	1

TABLE III. TIME—ADMISSION TO SURGERY
Series A

Less than 24 hours	16
Less than 48 hours	9
Less than 72 hours	8
Less than 96 hours	9
More than 96 hours	8

The time from admission to surgery is tabulated in Table III. One-half of the patients were operated upon within the first forty-eight hours; eight patients were operated upon between five and eighteen days after admission. This delay in their surgery was due to medical complications. Three patients had delirium tremens due to their acute alcoholism. Three patients had cardiac damage sufficient to delay their surgery until adequate management could be undertaken. One patient suffered a drug reaction and one patient developed pneumonia.

There were seven deaths in this series for an over-all mortality rate of fourteen per cent. The average number of hospital days was 18.1.

Series B.—The average age in this group was 55.2 years. The age distribution is tabulated in Table IV. The greatest incidence, again, as in Series A, is between the ages of fifty and seventy-nine. There was one patient under the age of twenty and one patient over the age of seventy-nine.

The quantity of blood given this group of patients ranged from 2,500 to 7,000 cc. The average was 4,000 cc. or 500 cc. more than in Series A.

The symptoms of the patients varied from two hours to four days prior to admission. The average was two days. Twenty patients (40 per cent) demonstrated melena only, fifteen (30 per cent) hematemesis only and fifteen (30 per cent) both melena and hematemesis.

TABLE IV. AGE DISTRIBUTION
Series B

0-19	1
20-29	1
30-39	4
40-49	7
50-59	17
60-69	10
70-79	9
80-	1

In this group the incidence of previous peptic ulcer history was 38 per cent. Only seven patients (14 per cent) had previously bled. There were two patients (4 per cent) with previous perforation. In ten patients (20 per cent) roentgenological demonstration of peptic ulcers had been made.

TABLE V. SOURCE OF BLEEDING
Series B

Duodenal ulcer	26
Gastric ulcer	14
Gastritis	5
Unknown	5

The source of the hemorrhage in this group is tabulated in Table V. Duodenal ulcers accounted for bleeding in twenty-six patients (52 per cent) and gastric ulcers in fourteen patients (28 per cent). In five patients no source of bleeding could be found and empirical gastric resection was carried out.

The time from admission to surgery varies in several important respects from Series A (Table VI).

TABLE VI. TIME—ADMISSION TO SURGERY
Series B

Less than 24 hours	0
Less than 48 hours	16
Less than 72 hours	19
Less than 96 hours	8
More than 96 hours	7

There were no patients operated upon in less than twenty-four hours. Sixteen patients were operated on within thirty-six hours and thirty-

five patients were operated on within seventy-two hours. Seven patients were operated on between five and sixteen days. This delay was due to indecision on the part of two patients to accept surgical therapy, to infectious processes which required treatment in three instances, to a thrombophlebitis developing at the site of a transfusion in one instance and to alcoholic delirium tremens in one instance.

The average hospital days in this group was 17.7 days. There were three deaths in this group for an over-all mortality rate of 6 per cent.

TABLE VII. AGE DISTRIBUTION IN 100 CASES

0-19	1
20-29	2
30-39	9
40-49	13
50-59	27
60-69	29
70-79	17
80-	2

TABLE VIII. SOURCE OF ACTIVE BLEEDING IN 100 CASES

Duodenal ulcer	56
Gastric Ulcer	26
Gastritis	11
Varices	1
Unknown	6

Combining Series A and Series B into a total of 100 consecutive patients, the data are tabulated in Tables VII, VIII, IX and X.

The over-all mortality rate for this series is 10 per cent.

Discussion

Series A represents a group of patients in which the criteria for "massive" gastrointestinal hemorrhage is somewhat vague. However, the criteria applied to this group are those criteria which have been used in assessing the presence of massive upper gastrointestinal hemorrhage prior to the use of plasma volume determination. This series, therefore, represents a group of patients who can be compared with previous series reported in the literature. That hemoglobin and hematocrit values are not adequate criteria upon which to judge a patient's operability is obvious. Undoubtedly some of the patients in this group were operated upon when their total plasma volume and red cell mass were far from normal. Also, the rate at which the transfusions were given did not coincide with the rate of blood loss and, therefore, did not permit good preoperative preparation.

The seven deaths in this series are worthy of discussion. Patient 4961 died on the fourth postoperative day of a subphrenic abscess. No source for this abscess could be found in either the suture line of the duodenal stump or the gastroenterostomy; however, it is assumed that such leakage did occur and that the over-whelming toxicity of infection precipitated his demise. Patient 2070 died on the third postoperative day following wound dehiscence and evisceration and pneumonia. Patient 2596 died on the fifteenth postoperative day of a subphrenic abscess. Patient 2650 died on the sixth postoperative day of bronchopneumonia. Patient 1067 died on the second postoperative day of an internal hernia of the small bowel. Patient 2725 died on the second postoperative day of a cerebral vascular accident. Patient 2831 died on the third postoperative day of massive atelectasis and thyrotoxicosis. These seven deaths represent probable technical errors in three patients and inadequate preoperative preparation of one patient. The three patients who expired due to evisceration and pneumonia and due to atelectasis and the cerebral vascular accident probably cannot be attributed to technical errors.

TABLE IX. TIME FROM ADMISSION TO SURGERY IN 100 CASES

Less than 24 hours	16
Less than 48 hours	25
Less than 72 hours	27
Less than 96 hours	17
More than 96 hours	15

TABLE X. MORTALITY RATE IN 100 CASES

Series A	14%
Series B	6%
Series A and B	10%

It became evident after reviewing the first fifty patients that improved preoperative management of this critically ill group of patients might well reduce the mortality rate. We were also impressed with the fact that the quantity and rate of transfusions were not adequately measured. By utilizing T-1824 vital dye we were better able to determine the quantity of blood needed by our patients and the rate at which this whole blood was to be administered. By repeating the

plasma volume and red cell mass just prior to surgery we were able to determine whether bleeding had continued while blood replacement had been carried out and to quickly replace this additional loss of blood just prior to surgery. In addition none of the patients were operated on within the first twenty-four hours in order to provide our medical colleagues with a better opportunity for full clinical evaluation. We had hoped by this to avoid early surgical intervention in patients with advanced cardiac disease and other controllable disease processes so that we might place these patients in a better state of operability.

In Series B there were three deaths. The first death, Case 6133, was the first patient in this series. He successfully underwent his preoperative blood replacement and subtotal gastric resection. He was well on his way to recovery when he rebled massively on the eighth postoperative day. He received twenty-seven units of blood in a period of approximately four hours. At reexploration the duodenal ulcer was found to be actively bleeding. The bleeding was controlled. However, the patient developed a wound dehiscence, wound infection and finally succumbed on his forty-first hospital day of acute yellow atrophy of the liver. Patient 77033 expired on the twelfth postoperative day of progressive hypotension which was not attributable to continued bleeding. No autopsy was obtained and it was assumed that his death was on a cardiac basis. Patient 77753 died on the fifth postoperative day of bronchopneumonia. It is interesting to note that all but the first death in this series were in patients who continued to bleed during their immediate hospital stay and were operated upon before optimal blood replacement had been given in order to attempt to control their acute hemorrhage. It was, nevertheless, gratifying in Series B to have reduced the mortality rate from 14 to 6 per cent. It is still more gratifying to know that this study extends beyond the confines of this report and that the over-all mortality rate is now less than 6 per cent.

With the availability of plasma volume determinations in all hospitals equipped with well run laboratories, the clinician has at his disposal a means of more accurately replacing the blood loss in a patient with massive upper gastrointestinal hemorrhage. In the hands of an experienced gastric surgeon, surgical principles may be applied to this clinical entity with an over-all mortality rate which approaches the mortality rate of elective gastric resection for peptic disease. With the experience gained in this group of 100 patients, the mortality rate has been reduced progressively from 14 to 6 per cent. Since the criteria of massive gastrointestinal bleeding applied to Series B is the most critical criteria applied to any series yet published, we feel that the over-all mortality rate is even more significant.

Conclusions

Gross bleeding into the upper gastrointestinal tract is a serious complication of peptic ulcer. The prolonged hypoxia from acute hemorrhage produces complications which increase the mortality and morbidity rate. The diagnosis of gross bleeding can be made with considerable ease and its quantity with reasonable accuracy. The surgical arrest of such bleeding and the treatment of the ulcer diathesis can be carried out with a relatively low mortality rate.

WHO REPORTS ON SALK VACCINE SURVEY

According to the report of the World Health Organization's study group on poliomyelitis vaccination, the United States is the only country which showed ill effects from polio vaccinations, with some of its cases traceable to faulty vaccine batches. In all, approximately 10 million children were vaccinated against polio with no subsequent effect. In addition, the study group noted that although no definite immunity period has been established in connection with Salk vaccine, it has given good protection to children between the ages of six and ten.

Norway, Sweden, South Africa, Canada, Denmark, France, Germany, the United Kingdom and the United States participated in the WHO study group meeting in Stockholm. The 40-page summary report they issued contains recommendations regarding the use of polio vaccine and is intended as a guide to world health authorities "who may be considering whether or not to begin polio vaccine programs." Topics of the report include the application of stringent safety tests; the seriousness of an existing polio situation in a country and the cost of a vaccine program in relation to available funds, timing of a vaccine program and utilization of virus strains.

Hookworm Treatment of Polycythemia Vera

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FOREIGN authors[1,2,3] have utilized hookworm for therapy of polycythemia vera. The low-grade symptomless blood loss due to this intestinal parasite theoretically sounds reasonable for relieving these patients of their plethora. This form of treatment has been given to one patient with a satisfactory result in a fourteen-month follow-up. To the best of our knowledge, this is the first use of this treatment in the United States.

Case Report

The patient was a fifty-one-year old white woman, a school teacher in whom a diagnosis of polycythemia vera was made in 1937. At that time she had an enlarged liver and spleen. For the following fourteen years she was treated with phenylhydrazine and venesections. She was first seen by the senior author in March, 1951, when she was quite weak but actively teaching school, with a hemoglobin of 9.9 grams per cent (Evelyn) and a hematocrit of 35. There were 11,100 leukocytes, with 84 per cent neutrophiles, 2 per cent eosinophiles, 13 per cent lymphocytes and 1 per cent monocytes, and 3.55 million erythrocytes. Bone marrow studies revealed a normoblastic hyperplasia without any evidence of leukemia. Phenylhydrazine was discontinued and in five weeks the hemoglobin was 17.7 grams per cent. The highest hematocrit recorded was 65.

Venesection therapy was begun again. In the eight months remaining in 1951 she had removed by venesection 1,900 cubic centimeters of blood; in 1952, 3,200 cubic centimeters of blood; and, in 1953, 2,000 cubic centimeters of blood. The time of venesections was largely determined by symptoms of the patient and, in general, venesections were done when the hematocrit was over 55. The lowest hematocrit was 45, and at this time the patient was quite weak and quite short of breath, especially after climbing stairs. She would plan to have her venesections on a Friday so that she could recover in bed to be back at school teaching on Monday. Before the venesections she was generally extremely uncomfortable and complained of headaches, fullness in the head, unsteadiness, clumsiness, feeling flushed and weak with scattered paresthesias over her body.

On January 29, 1954, she gave 500 cubic centimeters of blood by venesection. On February 4, 1954, there were 14 grams per cent of hemoglobin (Evelyn) with 8.04 million erythrocytes; a hematocrit of 53; 16,500 leukocytes with 81 per cent neutrophiles, 13 per cent lymphocytes, 1 per cent monocytes, 4 per cent eosinophiles, 1 per cent basophiles; reticulocytes 0.9 per cent; platelets 401,000; MCV 66; MCH 17; and MCC 26 per cent. Two hundred and sixty *Ancylostoma duodenale* larvae were administered percutaneously.

The source of the hookworm larvae was a native of Iraq, and the parasites were identified as *Ancylostoma duodenale* by the unequal esophageal spears and the close approximation of the anterior end of the intestine and the esophagus in the infective larvae.

A stool specimen was mixed with powdered charcoal and incubated at room temperature for two weeks. The mixture was then placed in a Baermann funnel and the infective larvae were collected. The larvae were filtered out of the suspending water and the filter paper, with the larvae down, was again placed on five layers of gauze on the screen of a Baermann funnel and the larvae were collected a second time in clean water. The glassware used was heat sterilized but no further precautions against possible bacterial contamination were taken.

The larvae were suspended in 15 cc. of water, and from counts of 1/10 cc. samples an estimate of 260 larvae was made. The suspension was poured on a 3-inch disc of white blotting paper which was laid upon the patient's left thigh for one hour. The patient noticed a very mild local itching during the exposure and that evening more of the itching occurred. For the next ten days there was a swelling and thickening of the inoculation site with a hive-like formation that persisted for ten days.

Very shortly after this, the patient developed an upper respiratory infection as manifested by coryza and a sore throat. On February 22, 1954, she developed hoarseness and a "different" sore throat and frequently ran 0.2 degrees (F) of fever. This persisted for two weeks. On March 5, 1954, or one month after the administration of the larvae, she developed a severe night cough productive of a small amount of tannish sputum which persisted for one month. Then for nearly one month more she had a cough in the daytime productive of grey sputum. The patient was examined at weekly intervals and there were no abnormal findings in physical examination of the chest. On March 12, 1954, a chest x-ray showed findings interpreted as peribronchiolitis or perhaps a faint subsiding pneumonitis in the left lower lobe.

On March 26, 1954, or approximately six weeks after

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TABLE I.

Date	Hemoglobin Grams Per Cent	Hematocrit	Leucocytes Per c.c.	Eosinophiles Per Cent
4 Feb 54	14.0	53	16,500	4
12 Feb 54	14.8		22,800	3
22 Feb 54	15.1	53	21,800	2
5 Mar 54	15.2		23,500	10
12 Mar 54	14.3		25,200	15
19 Mar 54	14.8		18,600	15
26 Mar 54	15.0	54	17,300	20
2 Apr 54	15.4		23,000	28
15 Apr 54	15.0		21,200	31
4 May 54	14.4	55	19,450	30
27 May 54	15.3		17,750	21
7 July 54	14.6		28,700	44
9 Aug 54	15.0	54	33,400	36
17 Sep 54	14.9	54	26,600	26
5 Nov 54	14.8	54	21,400	35
29 Dec 54	15.0	55	27,000	22
9 Feb 55	14.6	51	26,000	22
15 Apr 55	15.3	55	27,500	25

the administration of the larvae, the patient noticed morning nausea with very occasional emesis. Her appetite decreased in general and especially for sweets. This lasted perhaps two weeks. In May, 1954, or approximately four months after the administration of the larvae, for one to two weeks she had two to three loose bowel movements per day. On June 1, 1954, with school in recess, she lost all symptoms, and began to feel very well, indeed better than she had felt in many years.

The ova first appeared in the stools eleven weeks after exposure and were then too few to quantitate. After eighteen weeks 1,100 ova were counted. Since then monthly counts have averaged 3,500, the highest figure being 5,200. The benzidine test has been intermittently negative to three plus and the Guaiac has generally been negative, although once it was three plus. We have estimated that she has fifty to seventy hookworms.

At the beginning of this therapy the hematocrit was 53, and fourteen months later it was 55 without venesections (Table I).

Résumé and Discussion

An intelligent female patient with polycythemia vera, who had given 7,100 cubic centimeters of blood by venesection over the previous three-year period, was given 260 larvae of *Ancylostoma duodenale*. She developed minor itching, distress and hives at the inoculation area on the thigh; a few days later coryza and sore throat unrelated apparently to the hookworm; eighteen days after inoculation a "different sore throat" with hoarseness and a very slight fever; one month later a very severe night cough with tannish sputum; and for the next month a daytime cough productive of grayish sputum. Six weeks after inoculation she had minor transient morning nausea with very occasional emesis and a loss of appetite for sweets. Three months after inoculation for one to two weeks she had two to three loose bowel movements per day. Since then the patient has felt very well and is pleased with her treatment. She is very gratified by not having the discomfort associated with the high hematocrit before venesection and the discomfort and weakness for two to three days after venesection. The hematocrit at the time of the beginning of treatment was 53 and one year later it was 51. During the fifth month after giving the parasites, the eosinophil count reached 44 per cent.

Brumpt[1] feels that the usual sequence of events is that three days after inoculation there is migration through the lungs with coughing which occasionally lasts up to three weeks. Then in eight days the parasites are in the duodenum and there is epigastric distress, greatest at about one month, followed by diarrhea of from four to ten loose stools per day up to two months. He feels that the diarrhea is the biggest disadvantage of this form of therapy though it can be controlled by opium preparations. In his experience, decrease in red blood cell counts began in one month and complete effect was present in three months.

The most obvious disadvantage of this treatment in the fourteen months of observation was the one month of severe night cough with a lesser day cough for approximately one more month. The patient had a severe upper respiratory infection which began promptly after exposure to the parasite, and it may well be that the patient had a combination of a separately incurred pneumonia of a minor degree with the migration of the parasites through the lungs. Certainly the upper respiratory infection began before one would expect the migration through the lungs and the coryza would not be a part of the infestation.

Epidemiologically the therapy is acceptable.

Advantages of this form of treatment appear to be that it is simple, inexpensive, and there does not appear to be need for detailed supervision or special laboratory facilities as for venesections or radio-active phosphorus therapy. There is a slow regular fall in the red blood cell count while on a completely ambulatory regime. The therapy lasts five to six years and treatment can be terminated at any time. The disadvantages are considered to be the diarrhea which can persist up to two months but can be controlled by paregoric, and, in this instance, a severe cough was the only apparent disadvantage after fourteen months' observation.

This form of therapy should be considered for hemachromatosis.[4]

(Continued on Page A-40)

Eosinophilia in Malignant Disease

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EOSINOPHILIA, occasionally of high degree, may be found in association with malignant disease, as exemplified in the following case.

Report of Case

The patient, a sixty-one-year-old farmer, was examined at the Mayo Clinic in November, 1954. The patient stated that he had been perfectly well until July, 1954. His previous medical history was irrelevant and his family history noncontributory. Early in July, 1954, influenzalike symptoms developed which consisted of generalized malaise, backache and a pleuritic type of pain in his chest. The patient had remained away from work for only three days, and on his return he was still plagued by migratory aches and pains, particularly low in the back. These symptoms persisted, and because the low back pain interfered with sleep, he consulted his doctor around August 1, 1954. Roentgenograms of the spinal column, stomach and colon were said to have been negative at that time. Two weeks later so-called indigestion, characterized by frequent eructations, flatulence and anorexia, developed for the first time. During his illness of four and one-half months' duration he lost approximately 10 to 15 pounds. Ten days prior to examination at the clinic a purpuric area appeared without trauma in the left forearm and this was followed by similar lesions on both legs.

Careful systemic review revealed that the patient had experienced a few night sweats and also two nosebleeds, the latter just prior to examination at the clinic. In addition on a few occasions he had noticed some blood in his stools. He was somewhat constipated and attributed this to a reduced intake of food.

Physical examination was not remarkable except for evidence of loss of weight and the purpuric lesions on both legs and one on the left forearm. In the center of each purpuric lesion there was a clear zone in which a thrombosed vein could be palpated. These lesions were interpreted as being due to segmental superficial thrombophlebitis. No abdominal masses were palpable and rectal examination gave negative results.

Laboratory studies were reported as follows: The urine was normal. The value for hemoglobin was 14.0 gm. per 100 cc. of blood; erythrocytes numbered 3,950,000 and leukocytes 13,400 per cubic millimeter of blood. The differential count of leukocytes showed lymphocytes, 9 per cent; monocytes, 4 per cent; neutrophils, 45 per cent; eosinophils, 37 per cent; basophils, 1 per cent; metamyelocytes, 3 per cent and myelocytes, 1 per cent. One normoblast was seen. The platelet count was 90,000 per cubic millimeter of blood. The sedimentation rate was 29 mm. in 1 hour by the Westergren method. The sulfobromophthalein test of liver function revealed 20 per cent retention (grade 2). The roentgenogram of the thorax depicted a small area of fibrosis in the base of the left lung but nothing otherwise significant. Roentgenograms of the stomach and colon were negative for lesions, and a roentgenogram of the lumbar vertebrae revealed a narrowed second lumbar interspace with localized hypertrophic change.

Examination of the peripheral blood smear revealed some hypochromasia, mild polychromasia, increased rouleaux formation and considerable eosinophilia. The platelets seemed slightly reduced in number. Many clumps of malignant cells which were foreign to bone marrow were found on examination of the bone marrow, establishing the fact that the patient had a metastatic malignant lesion.

The patient was advised of the findings and dismissed from our care on November 23, 1954. He died on January 8, 1955. His doctor wrote that at the time of the patient's last hospitalization, a rectal tumor was palpable for the first time. At postmortem examination done elsewhere, the rectum was involved with an annular neoplasm which had infiltrated the mesentery. No gross abnormalities of other organs were found.

Tissue was forwarded to the Mayo Clinic and reviewed by one of the pathologists, Dr. Baggenstoss, who commented that the sections taken from the rectum revealed a high-grade carcinoma infiltrating the entire wall and the perirectal fat. Carcinoma cells had replaced the mucosa in a few foci but there was actually more carcinoma in the wall than in the mucosa. Most of the cells were in sheets and clumps, but in an occasional area glandular formations suggested that the lesion was an adenocarcinoma, grade 4, probably arising in the rectum. There were large areas of necrosis of tumor cells.

Sections of pancreas revealed a moderate degree of acinar dilatation but they were otherwise not remarkable. Sections of liver and spleen presented evidence of active extramedullary hematopoiesis with mitotic figures in the hematopoietic foci.

Comment

This case has three especially interesting aspects: First, the association of superficial, segmental thrombophlebitis with primary carcinoma in the

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rectum is highly unusual. Such lesions are much more frequently associated with carcinoma of the pancreas, particularly carcinoma of the tail of the pancreas, and with other retroperitoneal malignancies. Their occurrence in carcinomas of the stomach and lung and in malignant lymphomas has been noted also.

The association of a high percentage of eosinophils with a malignant lesion of the gastrointestinal tract also is unusual. Such an association was rarely commented on in the American literature until 1946, when Isaacson and Rapoport[1] reviewed the literature dealing with this subject. They collected nineteen cases of pronounced eosinophilia with cancer in which more than 10 per cent of the leukocytes were eosinophils. In addition, these authors added fifteen new cases of malignant tumor in which marked eosinophilia occurred. In twenty-seven of their thirty-four cases (79.4 per cent) metastasis had occurred. In two of the other seven cases, metastasis was not proved but was suspected. In one case metastasis was neither proved nor suspected. In the other four cases the report did not give sufficient information to determine the presence of metastasis. In seventeen of the twenty-seven cases in which metastasis was proved, hepatic involvement was noted. In twenty-nine of the thirty-four cases the malignant lesions were of epithelial origin, and in five they were of connective-tissue origin. Cases of carcinoma of the uterus, cervix, breast, penis, thyroid, adrenal pancreas, lung, stomach, gallbladder and colon as well as four cases of sarcoma were included in the group. Carcinoma of the colon was present in seven of the thirty-four cases, the largest number in a single organ. Isaacson and Rapoport[1] concluded from their study that the occurrence of eosinophilia with malignant tumors was usually indicative of dissemination and a poor prognosis.

Stickney and Heck[2] in 1944, in a general discussion on eosinophilia in which more than 6 per cent of the leukocytes are eosinophils, reported on a total of 418 cases. In tabulating the cases by degree of eosinophilia, they found malignant lesions in 5 per cent of the group in which 6 to 10 per cent of the leukocytes were eosinophils, 1.3 per cent of the group with 10 to 20 per cent eosinophils and in 4 per cent of the group with 20 per cent or more eosinophils. The type of malignant tumor was not specified in this report. Grewe and Schlitter[3] in Berlin in 1954 found among 800 cases of tumor 197 instances of eosinophilia in which more than 5 per cent of the leukocytes were eosinophils.

The cause of eosinophilia associated with malignant tumors remains obscure. Necrosis of the primary tumor or of a metastatic lesion is considered by most workers to play some role in the production of eosinophilia. It is postulated that the necrotic malignant tissue liberates protein degenerative products to which the individual has an allergic susceptibility. Although necrosis may be responsible in some way for the eosinophilia in many cases, this mechanism does not always explain the cause. Hepatic metastasis is frequently found when malignant disease is associated with eosinophilia, but the liver is not involved in all cases. The role of the liver in the production of eosinophilia is still poorly understood.

The final point of interest in this case was the leukemoid blood picture, which superficially at least might have been confused with leukemia. Metastatic malignancy, particularly when bone is involved, results in a peripheral blood picture that includes anemia, myeloid immaturity and normoblastosis. The common morphologic changes are increased rouleaux formation, toxic changes in the polymorphonuclear leukocytes, a scattering of immature myeloid cells, and one or more normoblasts. Anemia when present is ordinarily normochromic and normocytic. Low-grade leukocytosis is most commonly found, although fairly high counts can occur. In a patient with a known malignant tumor, the finding of this sort of peripheral blood picture must be regarded as evidence that the malignant tumor has metastasized, in the absence of other possible causes.

Aspiration of bone marrow may provide the simplest and most practical method of establishing the diagnosis. The importance of finding clumps of cells foreign to the marrow in smear preparations should be emphasized before a morphologic diagnosis is made. Diagnoses from single cells should be avoided. Confirmation can usually be obtained by examination of paraffin-fixed sections of bone marrow.

Summary

A case of carcinoma of the rectum is presented which is of interest because of the high degree of eosinophilia associated with it. Additional points

(Continued on Page 120)

Seminar

THE SYSTEMIC MYCOSES

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THE systemic fungous diseases are classified pathologically as infectious granulomas and present the same problems in diagnosis and treatment as do other members of this group, with certain additional difficulties due to their own characteristics. The deep mycoses are not contagious. With the exception of the less common acute forms, they tend to be insidious in onset and pursue a slow and smoldering course in which spontaneous remissions may occur. The diagnosis of tuberculosis is made fairly frequently in these conditions, for much of the clinical and laboratory evidence tends to be nonspecific and often misleading. It is becoming increasingly common for so-called tuberculomas to be later renamed granulomas, from which Histoplasma capsulatum, Coccidioides immitis or other fungi can be isolated.

The systemic mycoses form a circumscribed group because, with the exception of true actinomycosis, each of these diseases is caused by a single species of organism. Nevertheless, partly due to the inherent ability of these organisms to adapt themselves biochemically and morphologically to changes in their environment and partly due to failure to recognize the prevalence of these infections, treatment has not shown spectacular advances. Many agents that inhibit or kill the organisms successfully *in vitro* have proved to be too toxic when used in human patients in comparable doses. In the last few years, however, some promising agents have been used with good results in treating members of this group. Since wide-spectrum antifungal agents do not exist at present, it is essential that a precise and definitive diagnosis is reached before treatment is undertaken.

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For supporting evidence on which to base a diagnosis, the antibodies responsible for the state of hypersensitivity that develops in most mycotic infections may be detected by the use of cutaneous tests or may be quantitatively assessed by agglutination, precipitation or complement-fixation reactions. Once acquired, cutaneous sensitivity persists for many years and is then of little help in indicating the activity or quiescence of the disease. False positive results are frequent in sensitized persons if a high concentration of antigen is used, a circumstance that also favors a greater incidence of cross reactions, especially between blastomycin, histoplasmin and coccidioidin. False negative results often appear as an exhaustion phenomenon in the terminal stages of the disease, and the loss of established cutaneous sensitivity in known active mycotic infections may be of grave prognostic import, particularly if this is accompanied by increasing titers in the results of serologic tests. When difficulty exists in interpreting the results of cutaneous tests, help can be obtained from the serologic tests, a high titer indicating homologous cutaneous reactions and a low titer indicating that they are heterologous. Nevertheless, it is important to realize that these studies produce results which, at best, can be regarded only as suggestive or supportive. A diagnosis never should be made solely on the outcome of such tests.

Diagnostic evidence of a more direct nature is obtained from the microscopic examination of sections of tissue. The use of the periodic acid-Schiff stain has proved most effective in the identification of fungi in such specimens, although Gram's stain is to be preferred in demonstrating Actinomyces and Nocardia, whose filaments are gram-positive. Nevertheless, histologic examination has its limitations and various forms of Blastomyces dermatitidis, C. immitis and B. brasiliensis have been confused by experienced

mycologists. Inoculation of animals is of uncertain outcome and the most effective step in diagnosis is growing the organism on cultures made from pathologic material. Blood agar has been found to be the most satisfactory medium, with the addition, when necessary, of such antibiotics as streptomycin and penicillin to suppress bacterial contaminants. More specific media are required for certain fungi whose growth characteristics tend to be more fastidious. Final identification of the infecting agent rests on the results of culture of infected material, which should be sent to a laboratory properly equipped for the culture of fungi.

As far as general treatment is concerned, the iodides have remained the most useful therapeutic tool for many years, supported by more specific measures when such are available. Iodides may be administered orally as potassium iodide, intravenously as sodium iodide or by inhalation as ethyl iodide. Only in sporotrichosis can the iodides be regarded as specific.

Diseases Caused by Actinomycetaceae

The family Actinomycetaceae contains a varied group of organisms with characteristics intermediate between those of bacteria and fungi. They are world-wide in distribution and, before the advent of antibiotics, were responsible for the commonest of the systemic fungous infections in man. Two genera of medical importance are known. One is the parasitic, anaerobic and non-acid-fast Actinomyces and the other is the genus Nocardia, which includes organisms that are saprophytic, aerobic and variably acid-fast. Differences occur in the type of human infection that each produces.

Actinomycosis.—Human actinomycosis is caused by Actinomyces bovis or A. israeli, organisms that may be found around carious teeth, in the crypts of tonsils and in the gastrointestinal tract. They produce lesions characterized by fibrosis, the formation of granulation tissue, abscesses and multiple sinuses discharging pus in which the typical "sulfur granules" may be found. These granules are not invariably present; even when they are found, it is advisable to demonstrate the gram-positive filaments of the organism before one is certain of the diagnosis. Culture readily distinguishes the anaerobic Actinomyces from the aerobic Nocardia.

Sites of infection are in the cervicofacial region, the abdomen and the thorax in that order of frequency. In the face and neck, this disease often follows an old infection or the extraction of a carious tooth. Soft-tissue swelling, with lumpy wooden hardness and redness of the overlying skin, terminates in the development of discharging sinuses and possible involvement of bone. The abdominal form is commonest in the ileocecal region, where it may cause features suggesting acute or subacute appendicitis, with the formation of a hard mass in the right lower quadrant. Vertebral and hepatic infection, cutaneous involvement and spread to the thorax may follow. While ingested organisms are presumed to cause abdominal infection, the aspiration of the fungus is the commonest cause of thoracic actinomycosis. Pulmonary lesions tend to occur bilaterally in the lower part of the lung fields, and the mediastinum is frequently involved. A hilar mass may simulate neoplasm. The symptoms are those of a mild nonspecific respiratory infection, with the production of blood-streaked mucopurulent sputum containing the infecting organism. Pleural involvement may be part of the picture and purulent effusion may develop but more frequently the thoracic wall is invaded directly and the familiar sinuses appear, discharging their pus on the surface of the skin.

Surgical exploration of the sinus tracts should be undertaken to permit adequate drainage; excision of as much diseased tissue as possible should be accomplished, including intestinal and pulmonary resection. Penicillin in large doses over a prolonged period is the drug of choice, either by itself or in combination with a sulfonamide. Patients who have not improved after this type of chemotherapy or who have relapsed after a suitable course of treatment may respond to administration of streptomycin, chlortetracycline (aureomycin), oxytetracycline (terramycin) or chloramphenicol in large doses given for long periods. Stilbamidine also has been reported to be successful in resistant actinomycosis.[1]

Nocardiosis.—Systemic nocardiosis is chiefly pulmonary in origin, the infecting agent being Nocardia asteroides. This fungus occurs freely in nature as a saprophyte, but it causes a pulmonary infection in man that resembles tuberculosis, with subsequent pyemia and formation of multiple abscesses in the lungs, brain, subcutane-

ous tissue and muscles. From the two last-named sites, sinuses may drain pus onto the skin but, unlike the situation in actinomycosis, sulfur granules are seen infrequently. Not only does nocardiosis closely simulate pulmonary tuberculosis clinically but the roentgenologic appearances of the thorax are also similar and the organism is often found in a bacillary acid-fast form in sputum, pus, cerebrospinal fluid and fluid from empyema. Culture of pathologic material is the definitive method of diagnosis. Results of serologic and cutaneous tests are of little diagnostic value in human nocardiosis.

Treatment is directed along the lines already indicated for actinomycosis, but the use of sulfonamides in nocardiosis is specific. Administration of large doses should be maintained for a considerable period and continued for several months after apparent cure of the disease. Although aureomycin and chloramphenicol have been shown to be more effective than sulfadiazine *in vitro,* they were of much less value in *in vivo* studies in mice.[2]

North American Blastomycosis

First described by Gilchrist, in 1896, this disease is limited to North America and has a geographic predilection for the region of the Mississippi River valley and the southeastern part of the United States. The source of infection and the mode of transmission remain obscure but the causative agent is Blastomyces dermatitidis, a fungus that grows well on all laboratory media in common use. The disease is a chronic cutaneous or systemic or combined cutaneous and systemic infection in which the most characteristic reaction to the organism is the production of abscesses and chronic inflammation, with formation of scars.

The primary cutaneous form appears commonly on an exposed surface of the skin, particularly the face and upper limbs. The first evidence of infection is a papulopustule that slowly spreads peripherally to form a sloping purplish-red border studded with miliary abscesses, from which pus may be obtained for examination and culture. Ulceration of the center is followed by scarring, and the disease may persist in this form for many years. Hematogenous and lymphatic spread rarely occurs from these lesions; however, should it do so, the prognosis is as grave as it is in systemic spread from any other site.

As is frequently the case in the disseminated form of the deep mycoses, the site of primary infection in systemic blastomycosis is usually the respiratory tract. There is nothing specific about the onset of the disease, for the clinical picture is that of a mild respiratory infection with low-grade fever and a failure to regress. Over a period of weeks or months, symptoms of toxicity develop, and purulent sputum with attendant hemoptysis is a prominent feature. Evidence of widespread lesions in other organs finally becomes apparent, the principal sites being the skin, subcutaneous tissue and bone, of which the vertebrae and ribs are involved most often. The cutaneous lesions at this pyemic stage resemble those of the primary cutaneous form. Liver, spleen, kidneys, central nervous system and prostate are commonly infected but, in contrast to histoplasmosis and South American blastomycosis, the gastrointestinal tract is usually spared.

The mediastinum is almost invariably involved. Pulmonary lesions at first tend to be unilateral and their roentgenologic appearance may suggest that of carcinoma. As the disease progresses, cavitative or miliary tuberculosis may be simulated.

While positive cutaneous and complement-fixation reactions are valuable presumptive evidence of blastomycosis, cross reactions with histoplasmin and coccidioidin are common. If simultaneous testing with all three antigens is carried out, the true condition is usually indicated by the most pronounced cutaneous reaction. Similarly, a homologous serologic reaction will be manifested by a high titer, whereas a low titer indicates a heterologous reaction. Final diagnosis rests on the demonstration of B. dermatitidis by culture of sputum, gastric washings, pus, cerebrospinal fluid, tissue obtained for biopsy and other pathologic material.

Use of the iodides combined with electrocautery or roentgen therapy has been the prescribed plan of treatment for many years, but recurrence has been common. Of the many other agents listed, only aureomycin appears to have any pronounced inhibitory effect on the organism but even prolonged administration apparently does not produce sufficient concentration to eradicate the organism from the tissues. Other antibiotics have proved of little value. In 1948, however, it was found that one of the aromatic diamidines in

low concentration caused inhibition of the growth of pathogenic fungi *in vitro*.[3] This was stilbamidine, a drug that has been used for many years in the treatment of kala-azar and that has been given with variable success in the management of multiple myeloma. Clinical trials of this drug in the treatment of the mycoses have been most encouraging.[4]

The chemical analogue 2-hydroxystilbamidine has an equivalent inhibitory effect on the growth of B. dermatitidis and good results have followed its clinical use in systemic blastomycosis. It shows no significant change after exposure to ultraviolet light and does not produce trigeminal neuropathy even after sustained administration. As with stilbamidine, however, it should be used cautiously in the presence of renal or hepatic damage. Use of 2-hydroxystilbamidine undoubtedly is the treatment of choice in systemic North American blastomycosis. It should be given intravenously in a 5 per cent solution of glucose by slow drip and in divided courses. *In vitro* studies of various antihistamines, of diethylaminoethyl fencholate and of diethylstilbestrol have shown these substances to be satisfactorily inhibitory for B. dermatitidis. Unfortunately, *in vitro* trials and clinical results are not always parallel but diethylstilbestrol has been used effectively in the treatment of cutaneous North American blastomycosis. Isolated pulmonary lesions are suitably treated by surgical resection.

South American Blastomycosis

This disease occurs most commonly in Brazil and is almost confined to South America, although one case has been reported from Costa Rica[5] and an account of the first recorded instance in the United States has been published recently.[6] The latter patient was a resident of Oregon who had worked for a time in Venezuela. This form of blastomycosis is principally a disease of rural communities, although the fungus has not been isolated from the soil and natural infection in animals has not been demonstrated. The causative agent is B. brasiliensis, a multiple budding fungus that in certain forms is readily confused microscopically with B. dermatitidis. Cultures from infected material may be made readily on all common laboratory media, although growth is characteristically slow.

Coccidioidomycosis

Coccidioidomycosis is a dust-borne disease of the dry regions of the southwestern part of the United States, with its greatest prevalence in the endemic regions of the San Joaquin valley and other parts of California, Arizona, Texas, New Mexico, Utah and Nevada. It also occurs in parts of Central and South America. The causative agent, Coccidioides immitis, contaminates the soil in these endemic zones and is probably breathed into the lungs in dust during the dry summer and autumn months.

This primary infection is symptomless in a large proportion of cases, and only a positive cutaneous reaction to the injection of coccidioidin remains as evidence of contamination. If symptoms do develop, they follow an incubation period of about two weeks and are the nonspecific features of any febrile respiratory infection, in which pleural pain with or without attendant effusion also may be present. This picture often is followed in a week or so by the development of allergic manifestations in the form of erythema nodosum, erythema multiforme, phlyctenular conjunctivitis or arthritis of the knees and ankles. These signs of sensitization, which may develop after the asymptomatic form of primary infection, are associated with a good prognosis and systemic spread rarely occurs after they appear. Roentgenologic findings are extremely variable and films may show a midzone pneumonic process or circumscribed nodular lesions that may resolve, persist as large thin-walled cavities or undergo final calcification. Hilar or mediastinal glandular enlargement or minor degrees of pleural effusion also may be seen. Ulcerative nodular cutaneous lesions and lymphadenopathy, especially of infected nodes in the neck, either heal or progress to the systemic form of the disease. They form a nonpulmonary type of primary coccidioidomycosis.

Systemic spread of the disease occurs weeks or months after the primary infection. It is a relatively infrequent sequel of initial infection but it occurs with much greater frequency in colored persons than among Caucasians. The prognosis is grave and the expectation of life is little more than a year at the most. Symptoms of toxicity, high fever, wasting and occurrence of mucopurulent sputum appear as the organism spreads to infect subcutaneous tissue, bones, testes, me-

ninges and the viscera, with resultant formation of abscesses at these sites. The gastrointestinal tract is usually spared.

Results of precipitin and complement-fixation tests remain negative in asymptomatic and mild primary coccidioidomycosis but in severe primary infection the precipitin reaction becomes positive, reverting to negativity after a month or so. Complement-fixing antibodies appear late in severe primary infection and should disappear in a few weeks' time. Progressive increase in titer is good evidence of systemic spread. Results of skin tests with coccidioidin also become positive in all severe primary infections, and the cutaneous reaction thus induced may produce or aggravate the allergic symptoms attending the disease. As noted previously, cross reactions with blastomycin and histoplasmin may occur, and means for differentiating the three diseases already have been discussed. Confusion between inactive forms of C. immitis and B. dermatitidis may occur on microscopic examination of infected material. Culture of pus, sputum, gastric washings, cerebrospinal fluid, tissue taken for biopsy or other pathologic material provides the final diagnosis.

Large cystic cavities present in the lungs may be treated surgically, especially if recurrent hemorrhage occurs from them. Depending on the size, number and location of such lesions, anything from wedge resection to pneumonectomy may be required. Medical treatment of the primary form consists of rest in bed and supportive therapy, with adequate assurance that the leukocyte count, erythrocytic sedimentation rate, clinical and serologic findings and roentgenologic appearances have returned to normal before everyday activity is resumed.

In treatment of the systemic form of the disease, many drugs, including iodides, various dyes and heavy metals and antibiotics have been tried without success. Recent *in vitro* studies have shown that stilbamidine, certain antihistaminic drugs, actidione, prodigiosin, ethyl vanillate, methyl testosterone and the more toxic protoanemonin possess promising inhibitory properties. Clinical trial of protoanemonin did not produce encouraging results[7] but the use of prodigiosin, a purple dye extracted from cultures of Serratia marcescens (Bacillus prodigiosus) by organic solvents, has shown good results in six of fourteen patients, of whom five were moribund before treatment was commenced.[8] In general, those who showed improvement or arrest of their disease showed an absence of organisms in cultures in two weeks and healing of abscesses in about a month. Arrest of the disease was obtained in one patient who had systemic coccidioidomycosis treated with a combination of methyl testosterone and sulfonamides.[9]

Cryptococcosis

Cryptococcus neoformans, also known as Torula histolytica, causes a subacute or chronic infection of the central nervous system in man, although the lungs, solid viscera, skin and, occasionally, bone also may be attacked. This fungus occurs in nature as a saprophyte and may be isolated from the soil in many widespread regions throughout the world. Because it is a budding fungus, the infection it causes sometimes is designated "European blastomycosis," which is a misnomer in view of the fact that the disease is of world-wide incidence. The organism is one of the most indolent of the fungi, and chronic inflammatory changes and formation of pus are rarely caused by its presence. The typical lesions have a characteristic gelatinous character, with cystlike zones present in the substance of the brain from which the thick-walled budding fungus with its wide refractile capsule can be recovered. Culture of cerebrospinal fluid, sputum, gastric washings, exudates or tissue taken at biopsy on Sabouraud's medium or blood agar provides the final diagnosis. Cutaneous and serologic tests are of no help in evaluating the individual case, although specific polysaccharides have been demonstrated in the capsule of the organism.

The mode of entry of this fungus into the body is uncertain but the respiratory tract is the most likely pathway, although the skin, nasopharynx and other tissues have been incriminated. Primary or secondary cutaneous forms appear as acneiform or ulcerative lesions, while subcutaneous tumors or enlarged lymph nodes may be found, especially in the systemic form of the disease. The primary cutaneous lesions may heal spontaneously or later spread to initiate systemic dissemination of the fungus. The pulmonary form has little specificity in the way of symptoms to raise suspicion of its cause. It tends to be bilateral, although unilateral lesions may be encountered and are then suitable for surgical resection. The

roentgenologic appearances are usually confused with those of neoplasm or tuberculosis, although cavitation is not frequent. Miliary lesions are noted with widespread infection, although neither mediastinum nor bone is involved in most instances, a feature that is in sharp distinction to the findings in actinomycosis, coccidioidomycosis and North American blastomycosis.

The usual form of cryptococcosis involves the central nervous system and is probably always secondary to a site of infection elsewhere in the body, in most instances the lungs. Its characteristics are those of any subacute or chronic meningoencephalitis, with the features of severe headache, nuchal stiffness, vomiting, palsies of various cranial nerves and mental disturbances of severe degree. Death occurs in a few weeks or months from respiratory failure. Cryptococcosis is a systemic disease attended in its course by remissions of variable length and with the local manifestations already mentioned.

These natural remissions make it difficult to assess the efficacy of new forms of treatment. Treatment has been unsatisfactory and the sulfonamides do not appear to have fulfilled their early promise. Iodides and penicillin are of little value, and vaccines also have failed to influence the course of the infection. Streptomycin and quinacrine hydrochloride (atabrine) have been too toxic in the doses required. Protoanemonin, a synthetic lactone that is effective in the treatment of local lesions, has produced neurotoxic symptoms severe enough to preclude its use in systemic disease. A potentially more promising development has been the isolation of substances from the broth of cultures of Bacillus subtilis or of Pseudomonas aeruginosa that inhibit the growth of C. neoformans *in vitro*. Several antihistaminic compounds, as well as the afore-mentioned antifungal agent diethylaminoethyl fencholate, have similar well-marked *in vitro* properties and may be worthy of clinical trial.

Actidione, a substance isolated from culture filtrates of Streptomyces griseus that, unlike streptomycin, is soluble in organic solvents, apparently has produced favorable effects on the course of proved cryptococcosis, although unequivocal cures have not been reported.[10] Although the temperature curves and clinical courses were slightly improved in a series of ten treated patients, most of them died. In two others, the cerebrospinal fluid remained sterile for two months after treatment with actidione.[11] These results are neither substantial nor sustained but, for want of a better drug, actidione may still continue to be used in this disease. Nausea and vomiting have been the only observed side effects. The use of fever therapy has been suggested as an adjuvant, since a higher body temperature artificially induced in mice has been shown to enhance their resistance to infection by cryptococci.[12]

Good results have been obtained after the surgical resection of focal pulmonary lesions when the stigmas of systemic dissemination could not be found.

Histoplasmosis

It was noted about a decade ago that many people living in the central Mississippi River valley and in the Ohio River valley had extensive pulmonary calcification with negative cutaneous reactions to tuberculin and coccidioidin but positive cutaneous reactions to histoplasmin. It is now accepted that histoplasmosis is not the invariably fatal condition it once was thought to be. In fact, it closely resembles coccidioidomycosis in being a highly infectious primary pulmonary disease that often is asymptomatic and that undergoes systemic dissemination in a minority of cases. Pulmonary calcification is a common sequel and tends to be diffuse and bilateral. It may be confused with healed tuberculosis or coccidioidomycosis.

The offending agent is Histoplasma capsulatum, an organism of world-wide incidence that has been isolated from the soil of endemic zones. It has a special affinity for the cells of the reticuloendothelial system, the disease thus being a reticuloendothelial cytomycosis. Cryptococcosis, North American blastomycosis and tuberculosis have been found in association with histoplasmosis, and it would appear that a reinfection or reactivation form of histoplasmosis may occur. After entrance of the organism, cutaneous reactions to histoplasmin become positive and persist probably for life. Complement-fixation tests on the other hand regress from a positive reaction in high titer early in the infection to a negative reaction. Roentgenograms show multiple scattered pneumonic or nodular zones in both lung fields and hilar adenopathy in the majority of cases. Pulmonary lesions occasionally

are localized to one or two regions of a lung and may be amenable to surgical removal after the primary phase has passed. As already mentioned, multiple calcified foci are the residual evidence of infection by H. capsulatum.

The systemic form of the disease may follow a minority of primary pulmonary infections, but the primary site frequently occurs in the oropharynx or skin, where papules, plaques or punched-out ulcers are the common lesions. The intestinal tract also is a frequent portal of entry, especially in young children, with resultant ulceration of the lymphoid tissue of the small intestine. The clinical features of lymphadenopathy, hepatomegaly and splenomegaly are associated with pyrexia, emaciation, diarrhea, anemia and leukopenia. Involvement of the central nervous system and the development of solitary bony lesions are rare, although the organism can be obtained almost invariably on culture of the bone marrow. Even in the presence of widespread lesions, present opinion would lead to the belief that healing still may take place but, in general, the prognosis is extremely grave. A fading cutaneous reaction to histoplasmin and an increasing antibody titer are considered by some as indicative of serious progressive disease.

The organism can be obtained on culture of sputum, gastric washings, bone marrow, peripheral blood, tissue procured during biopsy of lymph nodes and other infected tissue on the usual media. Cross reactions may occur with blastomycin and coccidioidin in cutaneous testing but, as already mentioned, the largest reaction occurs with the homologous antigen. The same principle is followed in determining specificity when cross reactions take place in serologic tests.

Many agents have been tried in the treatment of histoplasmosis but none has met with unqualified success. The ethyl ester of vanillic acid inhibits the growth of H. capsulatum *in vitro*. Its greatest effect in animals occurs when it is given orally, suggesting that its main activity and possibly its toxicity are due to breakdown products of the drug. Toxic doses in mice cause inflammatory changes of the upper part of the gastrointestinal tract and glomerular and tubular damage in the kidneys, together with fatty degeneration and focal necrosis in the liver, toxic myocarditis and generalized capillary engorgement. The toxic dose in mice is one half its therapeutic dose. It causes drowsiness and apathy in infants; these symptoms disappear when administration of the drug is discontinued. Serious hyperventilation alkalosis of the type seen in adult encephalitis lethargica occurs in some children who are given this drug. Necropsy on persons thus treated who have died of histoplasmosis shows hepatic and renal changes similar to those found in laboratory animals. Despite these disadvantages and the added hazard of a narrow margin between toxic and therapeutic doses, ethyl vanillate has shown good results in some of the cases reported.[13] However, for the reasons already mentioned, interest in therapy with ethyl vanillate is diminishing. It is too toxic to use for any patients except those who otherwise face certain death.

Reports have been made of successful treatment of disseminated histoplasmosis with a combination of methyl testosterone and sulfonamides, with no toxicity noted during prolonged treatment.[9] Aspermia may be produced but this is reversible, as is the physiologic creatinuria resulting from its use. Jaundice was not present in the two cases reported. Report of a case in which diethylaminoethyl fencholate was employed leaves the efficacy of this drug in doubt, as other factors may have encouraged the healing process. It is not toxic and its *in vitro* inhibition of H. capsulatum is undoubted.[14] Antihistamines produce a similar effect in laboratory tests. Clinical trial of stilbamidine would not indicate any prolonged effectiveness of this drug in histoplasmosis.

As in the other systemic mycoses with isolated pulmonary lesions, surgical resection is the treatment of choice if no trace of further spread can be found.

Sporotrichosis

This is the only systemic mycosis in which iodides can be said to be specific. It is caused by Sporotrichum schenckii, which has been isolated from many natural sources, particularly soil, wood and plants, in all parts of the world. Infection follows trauma to the skin. Although the disease has been acquired from animals, there is no suspicion of spread from man to man. Unlike the other systemic fungous infections, the lungs are rarely, if ever, the site of primary infection, even in the disseminated form of the disease. The characteristic features of the localized infection

make its clinical diagnosis an easy matter, but it is virtually impossible in most cases to demonstrate the presence of the fungus either in sections of tissue or on microscopic examination of pus or infected material. Culture on Sabouraud's medium or blood agar is sufficient to provide the diagnosis, and the organism grows with ease. Antibodies can be detected in the serum by agglutination, precipitation and complement-fixation tests, and positive cutaneous reactions are obtained after the injection of a heat-killed vaccine or specific polysaccharide. These tests, however, are of more academic than practical importance. Prognosis is good except in the rapidly disseminated form and in the visceral type of disease.

In the commonest form of the disease, an exposed limb, most often the arm, becomes infected following trauma to the skin, in which wood, especially the barberry thorn, is frequently the incriminated agent. The primary lesion, granulomatous in nature, develops in the subcutaneous tissue at the site of injury and later involves the skin. Subsequently, the regional lymphatic vessels are involved, along the course of which ulcerating nodules occur; enlargement of the related lymph nodes takes place later. Thin pus ultimately is discharged from the ulcerating lesions, but dissemination rarely occurs. A polymorphous epidermal type of involvement also may be found.

The disseminated form of the infection, in which pulmonary involvement does not always take place, may be encountered without any primary site of infection being defined. Hard subcutaneous nodules appear over the surface of the body. These may enlarge but do not often ulcerate. The solid viscera may be involved, the most commonly affected being the kidneys, testes and epididymides. The bony skeleton is rarely a site of pathologic change in this condition but mucous membranes, especially of the oropharynx, often are involved in the disseminated form and also may be the seat of primary disease. Final diagnosis rests on culture of the organism from infected material.

Iodides are specific in sporotrichosis and some authorities consider that their action is a selective one on the fungus itself. Others think that they exert their action by stimulating a fibroblastic reaction and encapsulation of the organism. In the few instances of disease that is resistant to iodides, success has been reported after the use of sulfonamides, although other treatment has been favorably mentioned, including hyperthermia. Promising results were obtained after use of 2-hydroxystilbamidine in systemic sporotrichosis in mice but clinical trial produced more equivocal results in the one human thus far treated.[15] Surgical excision of local lesions is contraindicated, as it is followed so frequently by prolonged suppuration, but roentgen therapy in semi-intensive filtered doses is useful in the treatment of these surface granulomas.

Comment

It is not within the scope of this presentation to debate whether or not organisms of the genus Candida produce systemic infection in man. This fungus is such a well-known contaminant of devitalized tissue in all parts of the body that doubt has been cast on its ability to cause primary systemic involvement. Since the commonest manifestations of its pathogenicity occur in readily accessible and relatively localized regions, recognition is seldom difficult and treatment is confined to topical applications.

It is advisable to regard the use of cortisone in the systemic mycoses with benign suspicion at present, as it is uncertain how harmful its effects may be in allowing spread of the disease. On the other hand, it has been suggested that it may be of some value in tiding the patient over the initial acute phase of the illness.

The systemic fungous infections remain as diseases of protean clinical manifestations that are attended in most instances by a chronic course and in which final diagnosis depends on the cultural characteristics of the causative agent. It is extremely doubtful that any universally effective antifungal agent will emerge, at least in the foreseeable future.

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Current  Concepts

SMOKING AND THE CARDIOVASCULAR SYSTEM

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Today one of the major medical questions is, Does smoking really have an effect on the cardiovascular system of a man in good health? To answer this question, 425 standard smoking tests were carried out on 100 normal individuals. One would suspect little difficulty in determining the effect of smoking tobacco on the circulation of normal individuals. However, all methods of measuring blood flow in man are indirect. Some of the confusion in the results of smoking tests has arisen because too little attention has been paid to certain factors during measurement of peripheral blood flow. The most important of these factors are, (1) the environmental temperature, (2) the position of the subject, particularly the extremities, (3) the taking of food and (4) the basal metabolic rate. All must be considered whenever measurements of peripheral blood flow are made. The standard smoking test, as finally devised, used the skin temperatures as a measurement of blood flow, took into consideration the four factors just listed and also required simultaneous observations of blood pressures and pulse rates.

Sixty-six standard smoking tests* were carried out on six normal subjects, four physicians and two women technicians whose basal metabolic rates ranged from —17 to +1 per cent. These studies showed that the responses to smoking of the skin temperature of the same individual varied from day to day according to the basal metabolic rate, but the increase of the blood pressure and pulse rate during smoking varied little from day to day. Thus it was necessary to determine the basal metabolic rate and skin temperatures for each study. The skin temperature of the toes of all the subjects decreased an average of 2.5°C. (4.5°F.) with a range from 1° to 4°C. (1.8° to 7.2°F.) For the fingers the average decrease was 3.2°C. (5.8°F.). The average increase of blood pressure during smoking was 20 mm. Hg systolic and 14 mm. Hg diastolic. The pulse rate increased an average of 36 beats per minute ranging from 20 to 52 beats. The electrocardiographic changes consisted of increased heart rate, decreased amplitude of T waves with inverted T waves in one instance.

Habitual smokers did not show tolerance to the effects of smoking as the skin temperatures of the extremities decreased and the blood pressure and pulse rate increased. The decrease of the skin tmperature was not related to the length of time the subject had been a smoker or the number of cigarettes smoked a day.

Additional tests were necessary to determine whether the vascular changes were due to nicotine. Two groups of tests were made. (1) Normal subjects received a solution of sodium chloride intravenously as a control and then 2 mg. of nicotine was added to the solution without the subjects' knowledge. Here again the skin temperatures decreased rapidly and definitely, the heart rate increased and the amplitude of the T waves decreased. (2) Thirty smoking tests were carried out with various commercially available denicotinized cigarettes. The vascular effects were similar to those obtained when standard cigarettes were smoked. In order to determine how much the content of nicotine in a cigarette should be decreased to bannish the vascular effects, 192 standard smoking tests were done on 29 normal subjects between the ages of twenty and thirty-six years. Six different batches of cigarettes were

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*Two-thirds of two cigarettes were smoked and inhaled with the individual's accustomed depth and frequency.

Continuation Studies

GENETIC AND FAMILIAL ASPECTS OF CENTRAL NERVOUS CONDITIONS IN CHILDREN

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SO numerous and varied are the hereditary diseases of the central nervous system in children that an intensive course in human genetics could be fashioned around them. Unfortunately, there still is considerable disagreement regarding the identification and classification of such diseases. Many of the present-day recognized "entities" will undoubtedly prove to be groups of independent diseases. Genetic studies will very likely help in clarifying the multiple nature of such conditions.

There has been confusion in the past regarding genetic terminology, and this has been perpetuated by the majority of medical textbooks. Thus, the term "hereditary" was formerly used to designate dominant inheritance, in other words, the appearance of a particular trait in successive generations. "Familial" was used to indicate the multiple occurrence of a trait in siblings. "Hereditary" should instead be used to indicate that the trait in question is due to biochemical units which are customarily identified as genes. On the other hand, "familial" can be used to describe the greater-than-chance clustering of traits in families, regardless of whether heredity or environment is responsible for this phenomenon.

We can group the various diseases and anomalies into various categories according to their patterns of inheritance. On the one hand, we have several rather rigid types of genetic behavior, and on the other, what we might call "hereditary tendencies."

Ninety years ago, Gregor Mendel identified the patterns of dominant and recessive inheritance. Much has been learned since, particularly with regard to the nature of the underlying particulate bodies, the chromosomes and genes, but his basic principles continue to guide genetic thinking. Man has twenty-four pairs of chromosomes, twenty-three pairs being "autosomes" and one pair being "sex chromosomes." The latter pair consists of two "X" chromosomes in the female, and an "X" and a "Y" chromosome in the male. Like the chromosomes that "carry" them, the genes occur in pairs, the two paired genes being termed "alleles." Although "dominance" and "recessiveness" are now viewed as something less than absolute, we still find these terms to be of practical value.

A dominant gene is defined as one which produces its effect regardless of the nature of its gene-mate (allele). The "effect" will appear in all individuals possessing the gene. Muscular dystrophy of the facioscapulohumeral form often occurs as a dominantly inherited disease. An affected individual in such a case will pass the predisposing gene on to 50 per cent of his children, who in turn will develop the disease in adolescent years. In some dominant diseases, the bearer of the gene may sometimes not exhibit the trait. This is termed irregular or incomplete dominance, or lack of "penetrance." Thus, in epiloia (tuberose sclerosis) there will be a spotty appearance of the condition in the family pedigree. In such families there will be outwardly ("phenotypically") normal-appearing individuals, some of whom are inwardly ("genotypically") normal and some who are genotypically abnormal. Only the latter "normals" have the predisposing gene available to pass on to the next generation.

A recessive gene is defined as one which produces an effect only when present in double dose. In other words, the dominant allele must be absent. The bearer of a double dose must of course have obtained one such gene from each parent. The parents in such cases will usually appear normal, since they will ordinarily possess

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but one dose of the genes involved. Siblings subsequently born will have a one-in-four chance of getting a double dose of the gene. Since families are now usually small, recessively-determined hereditary diseases are frequently sporadic (only one in a family). It is in this type of inheritance that the parents search in vain for a taint in the family tree. When they learn that each of them evidently carried the predisposing gene, they are often relieved to know that neither one is solely to blame for the misfortune. Phenylpyruvic oligophrenia (phenylketonuria), a type of severe mental deficiency, is a classical example of this type of inheritance. Diagnosis of this disease is made by the testing of urine with ferric chloride. Recessively inherited traits are more likely to appear in marriages of blood relatives, since in such cases the parents tend to have more genes in common, the bad as well as the good.

A sex-linked gene is defined as one located on the sex chromosome. Such genes are usually recessive and usually located on the X-chromosome. This pattern of inheritance has been given widespread publicity because it is the pattern of inheritance shown by hemophilia. Female carriers of the gene appear normal since they ordinarily have a normal "cover-up" dominant allele present. The female passes the sex-linked gene on to 50 per cent of her sons, who then develop the trait because their Y-chromosome contains no cover-up allele. Progressive muscular dystrophy of the childhood type demonstrates clearly this pattern of inheritance. As the clinician is well aware, affected individuals are almost always boys. The few cases that do appear in girls may well represent a different entity. Gargoylism, though rare, has proved interesting in this respect, since it too is more common in boys. Clinically and genetically there appear to be two types of gargoylism, one type with corneal clouding and autosomal recessive inheritance, and another type with no corneal clouding and sex-linked recessive inheritance. Other types of sex-linked inheritance result if there is a dominant gene on the X-chromosome or if there is a gene on the Y-chromosome (the latter pattern then being from father to son, so-called holandric inheritance).

Not only may apparent clinical entities show different genetic patterns, but they may also be due to environmental factors. Such environmentally produced mimics are termed "phenocopies," a word coined by a geneticist working with fruit flies. Microcephaly is a good example, since it may be caused by a recessive gene, radiation during pregnancy, or by toxoplasmosis during pregnancy.

Many diseases "run in families," but show no distinct pattern of inheritance. In such cases, both heredity and environment may be involved. Even though no genetic ratios can be identified, it is possible to develop "empiric risk figures." In other words, if investigation is made of a large

TABLE I. HEREDITARY CENTRAL NERVOUS SYSTEM DISEASES AND ANOMALIES IN CHILDREN

Acrocephalosyndactyly: Heredity probably of importance.
Amaurotic Idiocy, infantile (Tay-Sachs' disease): Recessive.
Anencephaly: Incidence 1/1000. Risk for CNS anomaly in later siblings 2 per cent. Risk of abortion is 20 per cent.
Ataxia, Friedreich's: Generally recessive.
Ataxia, cerebellar: Generally dominant.
Cerebral diplegia: Some cases hereditary, probably recessive.
Epilepsy: Role of heredity in dispute, though generally agreed to be of some importance. Chance for recurrence in later siblings is around 2-3 per cent.
Epiloia (Tuberose sclerosis): Irregular dominant.
Gargoylism: Generally recessive, sometimes sex-linked recessive (no corneal clouding in such cases).
Hepatolenticular degeneration (Wilson's disease): Recessive.
Hydrocephalus: Incidence 1/500. Risk for CNS anomaly in later siblings 2 per cent.
Laurence-Moon-Biedl syndrome: Recessive.
Lindau's disease (Hemangioma of cerebellum and retina): Sometimes an irregular dominant.
Microcephaly: Some cases hereditary, being recessive.
Mongolism: Role of heredity is in dispute, though probably of some importance.
Muscular atrophy, progressive infantile (Wednig-Hoffman's disease): Recessive.
Muscular atrophy, peroneal: Dominant usually, but can be recessive or sex-linked recessive.
Muscular dystrophy, facioscapulohumeral: Usually dominant.
Muscular dystrophy, childhood progressive: Usually sex-linked recessive.
Myasthenia gravis: True congenital type may be hereditary.
Myotonia congenita: Dominant.
Myotonia dystrophica: Irregular dominant.
Neurofibromatosis: Irregular dominant.
Neurofibromatosis: Irregular dominant.
Oxycephaly: Sometimes recessive, sometimes dominant.
Paramyotonia: Dominant.
Periodic paralysis: Dominant.
Phenylketonuria: Recessive.
Schilder's disease (Probably includes a variety of diseases; exact classification in dispute)
Krabbe's disease: Recessive.
Pelizaeus-Merzbacher disease: Recessive, usually sex-linked?
Spina bifida: Incidence 1/400. Risk for CNS anomaly in later siblings 4 per cent.
Tremor, familial: Usually dominant.
Word blindness: Probably dominant.

number of families in which there has been born a child with a particular trait, the percentage of subsequently-born affected children can be determined. If there were 300 later-born children, and if fifteen showed the trait, then the empiric risk figure would be 5 per cent (or 1-in-20), and other mothers of such children could be told that subsequent children of theirs would have a 5 per cent risk of having the trait. In such circumstances the "entity" involved may well have multiple causative factors, and the individual pedigrees must therefore be evaluated carefully.

Although the genetically determined diseases and anomalies constitute a relatively small fraction of the central nervous system difficulties of childhood, the genes themselves are not really rare. Phenylketonuria occurs but once in about 25,000 children, but approximately one in every hundred individuals is a carrier of the gene. The carrier incidence is considerably higher for the more common recessive diseases.

A tabulation (Table I) has been made of the various hereditary and familial conditions of the central nervous system which present themselves in children. Except for several specific types, mental deficiency has been omitted, since it represents a poorly understood conglomerate of conditions. Although there are undoubtedly inherited susceptibilities to infections of the central nervous system, as has been shown for poliomyelitis, this subject has been omitted because environmental factors are so predominant. Also omitted are many of the rarer conditions, such as the recently described progressive familial infantile cerebral dysfunction in which the urine is said to have the odor of maple syrup. Likewise, the psychoses have been omitted, since they should be dealt with in detail if they are to be mentioned at all.

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SMOKING AND THE CARDIOVASCULAR SYSTEM

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used. The main stream of smoke from one cigarette of each batch contained respectively an average of 0.23, 0.55, 1.28, 1.83, 2.47 and 3 mg. of nicotine. As the concentration of nicotine in the main stream of the smoke was increased, the skin temperatures of both the fingers and toes decreased until the effects were the same as those from standard cigarettes. The lower the concentration of nicotine in the smoke the less the blood pressure and pulse rate increased from the basal level and vice versa. The increase was sharp when the concentration of nicotine was raised from 0.55 to 1.28 mg. Nicotine, then, has a most important rôle in production of the vascular changes which accompany smoking and these observations explain why the same vascular effects were obtained during the smoking of standard cigarettes and denicotinized cigarettes. Apparently, the content of nicotine in a cigarette must be decreased more than 60 per cent from that in a standard cigarette before smoking produces only slight or no vascular effects.

Since the oral administration of alcohol dilates the blood vessels of the extremities in contrast to the constriction from smoking, control smoking tests were made and on the next day the effect of smoking after the taking of alcohol was investigated. Eighty-seven smoking tests were made to determine the effect after ingestion of alcohol.† The blood pressure and pulse rate rose definitely on smoking after the ingestion of alcohol in 72 per cent of the subjects. The skin temperature of the fingers and toes decreased below the basal level on smoking after ingestion of alcohol. This seems to indicate that the alcohol did not prevent vasoconstriction from smoking.

†In the alcohol test 1 ounce of 95 per cent ethyl alcohol in fruit juice was administered orally and smoking was begun between thirty and sixty minutes after the ingestion at the height of the vasodilatation as measured by the increase in the skin temperature.

Editorials

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THE WRITTEN AND THE SPOKEN WORD

Much of the English that we hear nowadays and that we probably think of as spoken actually goes back to a written text. The President of the United States, for example, may seem to be talking informally in one of his fireside chats, but he is in fact reading from a carefully prepared manuscript. Even an interview that sounds very casual over the radio or television has probably been written out in every detail and timed to the half minute.

Thus, despite radio and television, writing is still important. Time over the air is too valuable to be subjected to the hazards of chance expression. When we wish to make sure that we have said what we wish to say as we wish to say it, we put it down in writing.

The study of writing within the framework of the communication skills has been helpful, however, in giving us a new point of view about writing and fresh approaches to it. "Good English" is no longer an arbitrary standard of formal and literary usage taught in the classroom but impractical elsewhere. It is English that is suited to a specific situation, and more often than not will be informal rather than formal.

Informal written English "lies close to current speech," to quote Porter G. Perrin, "but it is not, when written, speech exactly reproduced, partly because the written vocabulary is larger and somewhat more precise than the spoken. But its movement is largely colloquial, the movement of spoken English refined, tidied up, shorn of its looseness." This suggests that informal writing need not be regarded as such a highly specialized skill that communication between specialists and laymen must be left to the journalist as an intermediary.

Writing for others in the same professional field continues, for the most part, to be formal. The less specialized professional journals usually include both formal and informal writing.

It has been inevitable in a day of mass production that someone should have attempted to reduce the art of writing to a simple formula. The best known one is that devised by Rudolf Flesch and explained in his book *The Art of Readable Writing*. Although simple, readable writing cannot be achieved as mechanically and easily as Flesch would lead one to think, his book does give many practical, helpful suggestions about writing. Perhaps the chief value of prose engineering efforts such as Flesch's has been to encourage business and professional people to attempt to write for others outside their field. These efforts have also served to bring about a wider understanding of the relations between spoken and informal written English.

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GROUP THERAPY

Many recent advances in medical therapy have made headlines—polio vaccine, cardiac surgery, and similar gains. One form of therapy has crept into the armamentarium, less spectacular but of tremendous value. This is group therapy.

To some, the very name, group therapy, causes shudders; and while they feel it may not be as catastrophic as the H Bomb, the consequences could be almost as far reaching. It is realized that from time immemorial mass therapy has been a typical device of quackery, but the understanding of modern group therapy will remove any such association.

Group therapy might well be divided into those groups conducted by lay individuals and those under professional guidance with various degrees between them. Group therapy is applicable to children as well as adults.

The groups conducted by professionally trained individuals could have as their extremes on the one end, the pure analytical type, and the repressive inspirational on the other, with again, varying degrees between.

The leadership of these groups must be supplied by the individuals qualified for the specific type of group, the psychiatrist, psychoanalyst, psychologist, or physician interested in patients' problems.

There are those who feel that group therapy developed as an expedient to war-time conditions. The first authentic groups appeared in the very

early part of the century, and one of the first non-psychiatric groups appeared in this country in 1905 for tuberculous patients. The application of group psychotherapy to a subject for which it would appear almost specific, mental disorders, appeared in 1911. The psychoneurotic and psychosomatic conditions offer a most fruitful field for group therapy.

Group therapy has proven its values, and a study of the results reported from both psychiatric and non-psychiatric groups should allay the fears of those who shudder.

The dangers of group therapy lie not in the well-handled, well-studied groups, but in its adoption as a "cure yourself technique" unscreened and unguided. For those whose suspicions and prejudices cannot be overcome, one wonders whether "they are not throwing the baby out with the bath water."

HARVEY O. BEEK, M.D.

THE INTERNSHIP AND LICENSURE

There are growing stresses in many areas involving medical education and medical services. One of the vital areas on which much attention has been focused recently is the internship. In the symposium sponsored by the Council on Medical Education and Hospitals and presented before the Congress on Medical Education and Licensure a year ago, Dr. E. M. Leveroos of the Council Staff, provocatively issued the challenge that "the internship no longer provides sufficiently advanced educational opportunities and experience to justify its continuation as a separate and distinct phase of medical education."

Because internship is a legal requirement for licensure in some states and because of the National Board's demand for an internship prior to taking Part III of its examination, it may have been expected that licensing boards would have taken strong opposition to the challenge quoted above. Despite the pressure to shorten the total period of professional study and the criticism relating to rapid rotation through various services, four of the five panelists vigorously supported the value of the internship.

It is significant that those who supported the internship centered their defense around one major concept—that there must be a period following graduation from a medical school when the physician gradually assumes personal responsibility for definitive diagnosis and treatment. Dean Mitchell, in his discussion, referred to the internship as "a step that must be taken." The symposium, as published in the July 30, 1955, issue of *The Journal of the American Medical Association* clearly indicates the attitude of medical educators, specialty boards, and a representative cross section of the profession, the general practitioners.

There can be little doubt that, for purposes of providing time for assuming responsibility, the internship, through the years, has actually become an essential part of the total picture of medical education. The licensing boards have an interest in the internship because the true purpose of the licensing examination is essentially more practical than educational, and it attempts to cover the major branches of medical practice. Certainly, one of the major objectives of all education is to develop responsibility in the individual and, on this premise, educational effort must extend into the postgraduate area. Some of the present unrest in various state boards may represent a more critical interest in the appraisal of responsibility in the physician.

For the intern, the internship has two definite implications. First, as an essential "step," it should be considered an educational effort with a special purpose. Secondly, the intern should anticipate that his licensure examination will be largely a test of his fifth year in medical education.

The opinions expressed in the symposium are representative enough to illustrate that the internship is a vital link in the chain of events leading to the making of a competent physician. It may well serve, also, as a reflection of joint responsibility in the total field of medical education. The most important challenge involving internships is that they be improved.

S. D. EZELL, M.D.

RESEARCH AND THE PRACTICING PHYSICIAN

No one should appreciate the importance of research better than the practicing physician. Research provides the weapons and the ammunition with which he combats disease. He is peculiarly qualified to understand research. He has been initiated into its mysteries. He has trod the academic halls, been exposed to the laboratory, and learned the basic principles of science. He is

familiar with the vocabulary of science and can understand the purpose of research even when at times unable to follow its intricacies.

Research, simply stated, is man's search after nature's truths, insofar as he is able to discover them. *Basic research* seeks to increase our understanding of natural phenomena without promise of practical application. *Applied research* exploits discoveries for practical ends. The former is the bedrock of scientific advance, but may be pedantic and sterile without the latter. Applied research is empirical and often falacious without a foundation in basic research.

We live in an age of science. Our highly technological society is increasingly dependent upon the fruits of research—the discovery of fundamental principles and their application to practical problems. This dependence is reflected in the phenomenal growth of research. The growth curve clearly indicates the need for progressively expanded research efforts in the future.

The essentials for a productive research program are: adequate facilities and equipment, a suitable intellectual environment; adequate means of communication; and properly trained and highly motivated *brainpower*. Only one of these prerequisites, facilities and equipment, can be bought outright. The others require something more: insight and sympathetic understanding of research and those who follow a research career.

Winston Churchill is quoted as saying that science is no more than organized curiosity. Certainly, curiosity is a principal motivating force for those who choose a research career. All of us are curious in childhood as any parent can testify, but few of us retain this curiosity (or, at least, the initiative to satisfy it) as we grow older. Perhaps we tire of the effort, perhaps we are too busy making a living, perhaps we surrender in despair—there are so many things to know and to understand. But there are some who retain this childhood curiosity and are impelled to satisfy it; to them, the most important thing in life is the discovery of nature's secrets. These are the men and women we need in research. Every such individual who is diverted to another occupation is lost to science.

Essential for productive research is a favorable intellectual environment in which the investigator may work with a minimum of distraction. The atmosphere must be sympathetic to his needs. There must be opportunity for association with other investigators. The academic soil, with its opportunities for cross-fertilization, approaches the ideal.

Adequate means of communication is more than a local problem. The individual in research must be able to compare notes with his peers, to exchange experiences and ideas, to give and take in the friendly rivalry of comment and criticism. This is the life blood of research. Textbooks, monographs and scientific journals are helpful, scientific meetings more so, but intimate personal contact is most rewarding.

Finally, there is the matter of dollars and cents. Both facilities and equipment are increasingly complex and costs mount accordingly. The economic security of the investigator is a problem and more and more men are lost to research because of economic pressures. Total funds in support of research increase, but not in proportion to the need. If we must have the results of research, we must pay the price.

Cardiovascular research, with which this writer is most familiar, is an important facet of medical research. As such, it is governed by the broad principles of biological research, and has similar needs. Its achievements are no less than those of other medical researches, although they are sometimes overshadowed by the complex problems which remain.

One tremendous recent development is cardiovascular surgery. It becomes difficult to recall the days prior to the discovery of modern surgical techniques and ancillary developments. Mechanical hearts, hypothermia, improved anesthesia, cardiac catheterization and angiocardiography, and current methods for treating cardiac emergencies originated in the research laboratory.

Epidemiological research showed that rheumatic fever follows the ubiquitous streptococcal infection. Laboratory and clinical research established the usefulness of sulphonamides and antibiotics. It then became possible for the practicing physician to prevent rheumatic fever and rheumatic heart disease. One may now confidently predict that one day rheumatic fever will be eradicated.

Not long ago, the accepted treatment for most cases of hypertension was sedation and speculative advice. Then, briefly, surgery was the answer. Now we have a spectrum of helpful drugs, none of which is perfect, but which in the aggregate are

encouraging. The point is that there have been developments and advances. We look to research to find the cause of essential hypertension if we are to cure it.

Arteriosclerosis, specifically atherosclerosis, is the public enemy number one with which medicine has yet to deal effectively. We do not know its cause, empiricals have failed, and consequently, we can neither prevent nor cure it. Meanwhile, the study of this disease has mushroomed. Who can doubt the ultimate success of research here also?

Research's greatest need is for trained young people strongly motivated by curiosity. We must interest our youth in research, provide them with the opportunity to gain research experience and then help them become established in research careers. The practicing physician should be the most enthusiastic proponent of such a program. It is he who depends upon the weapons and the ammunition which research forges. It is he, also, who phrases many of the complex questions which stimulate the curiosity of the research scientist.

CHARLES D. MARPLE, M.D.
Medical Director
The American Heart Association

MEDICAL ETHICS IN ROUTINE PRACTICE

Each of our numerous medical societies has a committee called The Board of Censors. This is likely to be made up of men with vivid memories of their undergraduate and intern trials and financial tribulations. They are likely to assume that graduation from Class-A schools and fair internship ratings should be enough to exclude potential free-booters. This does not always work out ideally, but, for the most part, boards of censors have less to do with the qualifications of recent graduates than those members who are apt to travel from state to state and often represent interrupted and broken lives.

Recently, a well-domesticated elephant from a circus somewhere in the East decided to go on her own. Great disaster to the surrounding area and grief to the circus have followed up to date. Sharp hooks snagged into the animal's ears by exasperated keepers have not brought her back to the bosom of her feeding lot. A keeper in whom she has the utmost confidence is said to be the only hope for saving this worthy animal.

Perhaps this is not a dignified way to outline the work of a good board of censors or point the way as to how physicians may serve in a long medical life without being censored. It does focus attention, however, on three major premises: that an accredited graduate and licensed physician has been taught and guided by an ethically minded faculty; that the group, or medical society he wishes to join condones none of the evil practices that demean the guild as a whole; that the individual sets himself, without coercion, to fit into the field of honest medical practice and, as easily, gives example of normalcy as does the devoted husband in his conjugal relationships.

This is asking a good deal, but in a field as complicated as ours, it is noteworthy how few men deviate from normal standards despite the obvious fact that a few, through alcohol, drugs, or bad association, yield to the urge to defy our Hippocratic rules and allegiances.

EDWARD L. TUOHY, M.D.

INCOME MANAGEMENT

Family Service of Saint Paul has developed resources within its framework to assist families. These resources include Income Management, Homemaker Service and Temporary Child Placement.

For income management, families are referred to the agency primarily by employers or creditors when the families are not able to pay their bills and their wages have either been garnisheed or are threatened by garnishment. The service given in these situations for the most part is educational; however, some of these families need, and learn that they must have, help with their personal and/or marital problems before they can handle their indebtedness.

The request for this service is great. In 1954, more than $205,700.00 of families' own funds were handled through Family Service. The funds are disbursed in the following manner. With guides made available through the consulting home economist, a budget is made for the family. This is a low-cost budget which allows minimal

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This is sixth in a series on Family Service of Saint Paul —a Community Chest Agency. Family Service of Saint Paul has developed resources within its framework to assist families. These resources include Income Management, Homemaker Service and Temporary Child Placement.

essentials for the family. This amount is subtracted from the total income, and the balance is prorated among the creditors.

Often, Family Service must start by taking a wage assignment to prevent pressure from any one creditor's throwing the prorate out of balance. The family's earnings are mailed to Family Service by the employer. The amount previously decided upon jointly with the family for living expenses is returned to the family and the remainder is mailed to the creditors on a pro rata basis.

One question often asked is: What do these people buy that gets them into debt? At first glance, one is likely to think that the purchase of automobiles and television sets is the primary cause. It is true that the purchase of a used automobile that soon won't run without a great deal of repair and has to be turned in on another puts the debtor in the position of paying for two automobiles instead of one. However, most of these families who own automobiles need them in their work to provide transportation to and from work because public transportation is not available.

More than half of all indebtedness is for essentials, including doctor and hospital bills. Pressure put on by hospital management to pay the bill in full before the patient leaves the hospital drives families to small loan companies. This places an increased burden on the debtor because he pays 3 per cent per month on the loan. Oftentimes, on a prorate basis, the debtor is able to pay only the interest.

Family Service has facilities in casework staff and bookkeeping to handle approximately 120 families for money management at one time. Therefore, the number accepted for this service must be limited. Families with children are given priority, and those families whose income or situation is such that the job is in jeopardy if they do not receive help are accepted. In other words, Family Service concentrates on the "hardship" cases.

Families eligible for this service from Family Service of Saint Paul must live in Ramsey County or West Saint Paul, or the wage earner must be employed in a company that contributes to the Greater Saint Paul Community Chest and Council.

(Mrs.) Lois Hoffman
Director of Case Work Services

BANKS AND INVESTMENT SERVICES

Few people realize how many services are available in a bank's investment department in addition to the basic functions of a bank, such as accepting deposits for checking or savings accounts and lending money for various purposes. If one wants a plan for the building of an estate or permanent investment of an estate, there is no better place than a bank to consult representatives with long experience. This is true primarily in the larger banks or their affiliates. Whether the account is large or small, the knowledge and research facilities are invaluable in setting up lifetime plans with periodic servicing of accounts.

Is your income burdened with heavy taxes requiring tax exemption, or do you want more income to supplement earnings from your practice? These questions are normal, day-to-day problems in a bank investment department.

Do you want a balanced investment program with growth possibilities but with a certain amount of risk, or do you want assured income? This can be worked out to the individual's needs. If your present investments require a going-over to weed out the weaker securities to improve general quality, this can be done.

If you want principal maturing for education or other purposes, a bank can supply these needs. Or, if you just want to sell or buy, no place is more logical than a bank.

If you want to safely ship securities under a blanket insurance policy to practically any place in the country with a post office address (preferably to a bank), it can easily be done through a bank's investment department.

Bonds and stocks called for redemption or to be sent in for conversion are handled by trained employees with the "know-how" in expediting these functions.

Call features can be checked, dividends claimed, and transfers made with proper taxes determined. Liquidation of estates with security holdings are routine for the staff in a bank.

Many bank research departments have extensive files and available data covering government, municipal, industrial, public utility, railroad, and other types of securities. The need for providing pertinent and thorough information for the administration of trusts in a bank or trust company affiliate make available data which would be difficult to obtain from other sources.

A bank also acts for the United States Government in the distribution and collection of all kinds of Federal obligations. Questions regarding reissuance and changes can be answered readily in a bank.

BERNARD B. KNOPP
Manager, Municipal Bond Department
The First National Bank of Saint Paul

SICK LEAVE AND THE TAXPAYER

Periodically, we all need a stimulus to start us thinking—particularly along specific lines. Periodically, we all might do well to review our actions with an eye toward whether we want to maintain a reasonable standard of honesty, or whether we should be good fellows. Specifically, we are leading up to the matter of a physician's certification of the need for sick leave for a Civil Service employe, though the same principles will hold for any employe.

The whole matter is best expressed in a letter to the Secretary of the Massachusetts Medical Society from the Commander of the Boston Naval Shipyard, published in the December 8, 1955, issue of *The New England Journal of Medicine*. In it, the commander points out that: (1) a sick leave application is a legal document which forms the basis for the payment of government funds; (2) each day of unnecessary and unwarranted absence contributed to excessive costs and delays; and (3) unwarranted sick benefit payment, or padded or exaggerated vouchers, add to the tax burden of all citizens, and, in addition, constitute an element of fraud.

What with all our real concern about excessive governmental expenditures, we can afford to take a realistic attitude toward sick-leave certifications and sign them only when sickness or injury physically incapacitates the employe, when the sick leave is necessary for his health.

H.G.M.

NEW LOOK

Attention of our readers is called to the use of a different type face in MINNESOTA MEDICINE, Baskerville, which is considered a more readable type than that used in the past. Another change, instituted with the publication of the January, 1956, number, is wider spacing between columns of type on each page, giving a better separation between the two columns. This also was done in the interest of easier reading.

From time to time, other changes in the format will be made with the object of improving the journal both in attractiveness and readability.

THE SYSTEMIC MYCOSES

(Continued from Page 110)

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EOSINOPHILIA IN MALIGNANT DISEASE

(Continued from Page 102)

of interest were the occurrence of a leukemoid blood picture and the unusual clinical manifestation of segmental superficial thrombophlebitis.

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President's Letter

GROUP LIABILITY INSURANCE

The marked increase in malpractice insurance rates in 1952, and again in 1954, resulted in our Council's appointing a special committee to survey the entire field of malpractice insurance. On recommendation of this committee, the House of Delegates in May, 1955, voted to sponsor a group plan of liability insurance for Minnesota doctors, underwritten by the St. Paul-Mercury Indemnity Company.

At the same meeting, the Association also sponsored a group disability insurance program, and, though I believe both plans were explained to most of the component medical societies by our Mr. Harold Brunn, the group disability was pressed because it was necessary to have 50 per cent participation by a certain deadline to put the plan into effect. From numerous inquiries received, I feel some confusion exists and many doctors have forgotten the advantages of the group malpractice plan.

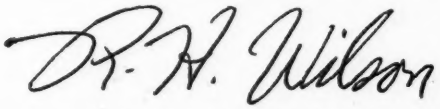
The advantages pointed out by the committee are, briefly: that increased volume of business by an experienced company will permit increased specialization of investigative personnel, defense attorneys, et cetera, needed for the peculiar problems involved in malpractice insurance; insurance will be available to members in good standing without the compulsion of buying other types of insurance to get it; an extensive and co-ordinated educational program of prophylaxis and control will be implemented; vigorous defense against all non-meritorious claims will be stressed with the purpose of eliminating the so-called "nuisance-claim settlements" which only lead to more future unwarranted claims.

The final and most important advantage is that it will afford close liaison between the insurance company and our Association in all matters, including selectivity of risks with possible exclusion of chronic offenders, furnishing of expert testimony in defense of these cases, and medical judgment as to whether a case should be defended in court or settled out of court. This same liaison will provide statistical facts and figures on which future rates will be based. This close liaison between the underwriters and the Association, in my mind, is the greatest advantage. Our Association has an exceptionally capable Medical Advisory Committee that has always been willing and anxious to serve any member threatened with a malpractice action, but they have too rarely had the opportunity. Under this plan, they will be in close consultation with the insurance company on all threatened actions and their knowledge, judgment, and experience will be invaluable.

The rates on the group plan will run about 5½ per cent lower than present standard rates. The more doctors joining the group, the greater will be the opportunity for more efficient and economic handling of cases. More important, a future reduction will be possible in the number of cases, and a corresponding probable reduction in rates.

This does not in any way involve any discrimination or condemnation of other plans or companies. It is simply that we believe that the plan and the company selected most suitably meet the needs of the Association at this time.

As our present liability contracts expire, I feel, in justice to each other and for the good of all, we should very seriously consider our Association Group Liability Insurance Plan.



President, Minnesota State Medical Association

Medical Economics

Edited by the
Committee on Medical Economics,
Minnesota State Medical Association
George Earl, M.D., Chairman

STATE OF THE UNION MESSAGE

The following comments do not indicate the official position of the American Medical Association on specific items of legislation proposed in President Eisenhower's third message on the State of the Union. Such measures may be commented upon intelligently only after examination of the specific bill. The quoted paragraphs are from the message; they are followed by a brief summary of the past position of the AMA on previous measures in the same area and are furnished for background information only.

"In the last analysis, our real strength lies in the caliber of the men and women in our armed forces, active and reserve. Much has been done to attract and hold capable military personnel, but more needs to be done. This year, I renew my request of last year for legislation to provide proper medical care for military dependents and a more equitable survivors' benefit program. The administration will prepare additional recommendations designed to achieve the same objectives, including career incentives for medical and dental officers and nurses, and increases in the proportion of regular officers."

The AMA believes that dependent medical care, if authorized by Congress, should primarily utilize civilian facilities and civilian physicians, with care to be furnished in military hospitals or by physicians in uniform only in overseas areas or where civilian resources are inadequate.

The AMA vigorously supports a career incentive program adequate to attract a sufficient number of physicians and dentists to voluntary service. Only in this manner can the necessity for some form of involuntary service be reduced.

"Closely related to the mission of the defense department is the task of the federal civil defense administration. We must strengthen federal assistance to the states and cities in devising the most effective common defense."

The AMA urges greater emphasis on the medical aspects of civil defense, with adequate appropriations to permit a realistic preparation for medical emergency produced by atomic, chemical or biological attack.

"Under the 1954 amendments to the old-age and survivors' insurance program, protection was extended to some 10 million additional workers and benefits were increased. The system now helps protect nine out of ten American workers and their families against loss of income in old age or on the death of the breadwinner. The system is sound. It must be kept so. In developing improvements in the system, we must give the most careful consideration to population and social trends, and to fiscal requirements. With these considerations in mind, the administration will present its recommendations for further expansion of coverage and other steps which can be taken wisely at this time."

The AMA urges a thorough, objective and impartial study of the economic, social and political impact of Social Security, both medical and otherwise, as the sole basis for objective non-political improvements in the Act. The AMA opposes the compulsory coverage of physicians under OASI, but does not oppose their inclusion on a voluntary basis similar to that permitted ministers.

"Other needs in the area of social welfare include increased child welfare services, extension of the program of aid to dependent children."

This is a part of the Social Security Act, a thorough study of which is urged as the sole basis for any further changes.

"The nation has made dramatic progress in conquering disease—progress of profound human significance which can be greatly accelerated by an intensified effort in medical research. A well-supported, well-balanced program of research, including basic research, can open new frontiers of knowledge, prevent and relieve suffering, and prolong life. Accordingly I shall recommend a substantial increase in federal funds for the support of such a program. As an integral part of this effort, I shall recommend a new plan to aid construction of nonfederal medical research and teaching facilities and to help provide more adequate support for the training of medical research man power."

The AMA has, in the past, been a supporter of properly administered research grants and supports one-time "brick and mortar" construction grants, on a matching basis, for medical schools. The AMA has opposed "research construction" grants unco-ordinated with other federal research or construction programs. The AMA also opposes

federal subsidies to educational facilities, when used for operation or maintenance, because of the virtual certainty of federal control of the institution.

"Finally, we must aid in cushioning the heavy and rising costs of illness and hospitalization to individuals and families. Provision should be made, by federal reinsurance or otherwise, to foster extension of voluntary health insurance coverage to many more persons, especially older persons and those in rural areas. Plans should be evolved to improve protection against the costs of prolonged or severe illness. These measures will help reduce the dollar barrier between many Americans and the benefits of modern medical care."

The AMA supports voluntary health insurance plans and is convinced that their rapid growth and expansion is proof of their ability to cover all risks which can be covered under an insurance principle. Federal reinsurance is opposed as unnecessary, unworkable except as a subsidy, and dangerous to the orderly development of sound voluntary health insurance programs.

"Other legislation will be proposed, including legislation for prepaid group health insurance for employes and their dependents."

The AMA supports the principle of contributory health insurance, on a voluntary basis, for federal employes.

"All of us share a continuing concern for those who have served this nation in the armed forces. The commission on veterans pensions is at this time conducting a study of the entire field of veterans' benefits and will soon submit proposed improvements."

The AMA urges the provision of the finest medical care possible to veterans with service-connected illness or disability, but opposes federal medical care for illness or disability unrelated to military service.

COST OF PROPOSED MEDICAL RESEARCH

The Department of Health, Education and Welfare will be able to present good arguments for increasing its $99 million medical research allowance by another $25 million. Also, the heady prospect of balancing the budget seems to have given administrators a happy feeling of, "After all, we can afford it."

Many departments of the government share this expansive attitude, but, it must be mentioned, the budget has not yet actually been balanced. Even if the increased revenues that are resulting from the current boom manage to balance the budget this fiscal year, there is nothing to guarantee these revenues will stay at a high level. And if they do not, will the same administrators who are asking for part of the increased revenue, volunteer to take a cut in appropriations? In Washington, it doesn't seem likely.

Health, Education and Welfare Secretary Folsom was asked whether his proposed new spending would fit into the balanced budget the Administration says it is trying to achieve. Yes, he said, if the present revenues continue. This, in spite of the fact that it costs $60 billion every year to run a government that is more than $280 billion in debt.

It is at least questionable whether a government that habitually spends more than it makes until it finally owes more than four times its current income, can "afford" new luxuries.

CANCER RESEARCH MAY BENEFIT

According to "Washington Report on the Medical Sciences," principal beneficiaries of new appropriations for medical research will be cancer, mental and heart research. These funds will be allocated through the National Institutes of Health, the Public Health Service research arm.

For the National Cancer Institute, the White House will ask Congress to approve $32,437,000; for the National Heart Institute, $22,106,000; for the National Institute of Mental Health, $21,749,000. Four other institutes that will share to a lesser extent are those for Dental Research, Arthritis and Metabolic Diseases, Microbiological and Neurological Diseases and Blindness.

The National Institutes of Health budget for operating expenses was doubled. This item covers basic research in several fields and research fellowships. Indications are that Secretary Folsom favors more emphasis on fellowship awards in addition to increases in basic research.

MILITARY DEPENDENTS' HEALTH INSURANCE

One of the first bills to reach the hoppers for the medical care of military dependents was introduced in the House of Representatives by Chairman Carl Vinson (Democrat, Georgia) of the House Armed Services Committee. Under

(Continued on Page A-38)

Reports and Announcements

MEDICAL MEETINGS

State

Minnesota State Medical Association, annual meeting, Mayo Civic Auditorium, Rochester, May 21-23, 1956.

National

American Goiter Association, Drake Hotel, Chicago, Illinois, May 3-5. Secretary, Dr. John C. McClintock, 149½ Washington Ave., Albany, New York.

American Association of Blood Banks, ninth annual meeting, Somerset Hotel, Boston, Massachusetts, September 3-5. Secretary, Marjorie Saunders, 725 Doctors Building, 3707 Gaston Ave., Dallas, Texas.

Chicago Medical Society, annual clinical conference, Palmer House, Chicago, February 28-March 1, 1956.

Mediclinics of Minnesota, postgraduate course sponsored by Academy of General Practice of Broward County, Fort Lauderdale, Florida, March 5-14, 1956.

International Meetings

Canadian Medical Association, Quebec, Canada, June 10-14. Secretary, Dr. Arthur D. Kelly, 150 St. George St., Toronto, Ontario, Canada.

Congress of International Anesthesia Research Society, Miami Beach, Florida, April 9-12. Write Dr. R. J. Whitacre, 13951 Terrace Road, Cleveland, Ohio.

Congress of International Society of Hematology, Hotel Somerset, Boston, Massachusetts, August 27 to September 1. Secretary, Dr. W. C. Maloney, 39 Bay State Road, Boston, Massachusetts.

Inter-American Congress of Cardiology, Havana, Cuba, November 4-10. Write Dr. Ramon Aixala, Apartado 2108, Havana, Cuba.

International Academy of Pathology, Cincinnati, Ohio, April 24 and 25. Secretary, Dr. F. K. Mostofi, Armed Forces Institute of Pathology, Washington 25, D. C.

International Congress of International College of Surgeons, Palmer House, Chicago, Illinois, September 9-13. Secretary, Dr. Max Thorek, 1516 Lake Shore Drive, Chicago, Illinois.

World Medical Association, Havana, Cuba, October 9-15. Secretary, Dr. Louis H. Bauer, 345 E. 46th St., New York 17, New York.

Tenth Inter-American Congress of the Pan American Medical Association, Mexico City, Mexico, April 15-21, 1957. Executive director, Dr. Joseph J. Eller, 745 Fifth Avenue, New York, New York.

BIBLIOGRAPHY OF MEDICAL REVIEWS

The Armed Forces Medical Library announces the publication in May of a *Bibliography of Medical Reviews.*

The bibliography, arranged by subject, will contain approximately 800 references to review articles in clinical and experimental medicine and allied fields which have appeared in the calendar year 1955.

Copies of the *Bibliography of Medical Reviews* will be available upon request to the Director, Armed Forces Medical Library, 7th Street and Independence Avenue, Southwest, Washington 25, D. C., in the order of receipt.

MINNESOTA SOCIETY OF NEUROLOGY AND PSYCHIATRY

"Psychiatric Aspects of Dysmenorrhea" will be the subject presented by Irving C. Bernstein, M.D., and John L. McKelvey, M.D., of Minneapolis at the regular meeting of the Minnesota Society of Neurology and Psychiatry at the Town and Country Club, Saint Paul, Tuesday evening, March 13, 1956.

FIRST INTERNATIONAL CONGRESS OF HUMAN GENETICS

The first International Congress of Human Genetics will be held in Copenhagen, Denmark, August 1-6, 1956. This congress is planned to cover all genetic aspects of normal and pathological characteristics in man. Any person interested in the subject of human genetics and especially of medical genetics is invited to take part in the congress.

Provisional program and further information will be sent on request. Write the Secretariat of the First International Congress of Human Genetics, University Institute for Human Genetics, 14 Tagensvej, Copenhagen, N., Denmark.

PROGRAM OF SURGERY FOR CONGENITAL CARDIAC MALFORMATIONS

A regional program of surgery for congenital cardiac malformations has been developed for out-of-state children through the joint efforts of the Children's Bureau of the United States Department of Health, Education, and Welfare and the Minnesota Crippled Children Services. The University of Minnesota Hospitals has been designated as the regional center for this surgery. A similar program for Minnesota children has been established by Minnesota Crippled Children Services, in collaboration with the regional program. In order to facilitate offering the services to Minnesota children, the University of Minnesota Hospitals will be used, for the present; however, plans are being made to include other Minnesota hospitals as participants in the program, provided that the hospitals are interested and have facilities available for this specialized service.

A detailed announcement is being forwarded to all the physicians, public health nurses, and county welfare agencies in the state. Inquiries about the program should be directed to Crippled Children Services, Medical Services Division, Department of Public Welfare, 117 University Avenue, Saint Paul 1, Minnesota.

CONTINUATION COURSES

The University of Minnesota announces a continuation course in *Endocrinology for General Physicians* which will be held at the Center for Continuation Study from April 9 to 11. Management of the more common endocrine and metabolic abnormalities will be stressed. Guest speaker will be Dr. Peter H. Forsham, associate professor of medicine and pediatrics, University of California Medical School, San Francisco. The course will be presented under the direction of Dr. C. J. Watson, professor and head, Department of Medicine.

* * *

A continuation course in *Gynecology for Specialists* will be presented by the University of Minnesota next April 12 to 14 at the Center for Continuation Study. The course will be presented under the direction of Dr. John L. McKelvey, professor and head, Department of Obstetrics and Gynecology.

* * *

Radiology for General Physicians will be the subject of a continuation course to be presented April 16 to 18 by the University of Minnesota at the Center for Continuation Study. Registrants will have an opportunity to interpret films and carry out certain techniques under the supervision of qualified instructors. Attendance will be strictly limited, and early application is essential.

MINNESOTA STATE BOARD OF MEDICAL EXAMINERS

230 Lowry Medical Arts Building
Saint Paul 2, Minnesota

F. H. Magney, M.D., Secretary

MINNEAPOLIS WOMAN SENTENCED ON ABORTION CHARGE

Re: State of Minnesota vs. Helen Hicks, also known as Helene Reznick, Mrs. Roberts and Mrs. Raynick.

On January 9, 1956, the above named defendant, twenty-two, formerly Helen Hicks of 3428 Columbus Avenue, Minneapolis, was sentenced by the Hon. Levi M. Hall, Judge of the District Court of Hennepin County, to a term of not less than one year nor more than four years in the State Reformatory for Women at Shakopee, Minnesota, on a charge of "pregnant woman attempting abortion." However, Judge Hall suspended the sentence and placed the defendant on probation for a period of two years. The defendant stated to the Court that she married Morris Reznick of Minneapolis in December, 1955. When questioned by Judge Hall, she admitted that she had performed an abortion on herself on or about June 15, 1954.

As the result of an investigation conducted in June, 1955, by officers of the Minneapolis Police Department and a representative of the Minnesota State Board of Medical Examiners, the abortion charge was lodged against the defendant and a warrant was issued for her arrest but the authorities were unable to locate her until November, 1955, when she was arrested in Chicago, Illinois. After being returned to Minneapolis, the defendant entered a plea of guilty to the charge against her before Judge Hall on November 12, 1955.

WOMAN'S AUXILIARY

RAMSEY COUNTY NEWS

Mrs. L. G. Culver

The Ramsey County Medical Auxiliary board members started the new year with a record attendance of twenty-seven present at the January board meeting. Reports given by the committee chairmen showed that the doctors' wives have not been idle the past month.

Mrs. H. F. Schroeckenstein, chairman of the Medical and Surgical Relief Committee, reported that twenty-five cartons of supplies were packaged and sent to the Maryknoll Missions and twenty cartons sent to the Episcopal Diocese.

Mrs. Ralph Olson, in charge of cancer dressings, and her committee have developed a very efficient "assembly line" in making the dressings. While the board members are attending their meeting, the committee is busy cutting and folding pads in an adjoining room. These dressings are then ready for the board members to stitch while the meeting is in session. Not only has this method proved profitable, but it is also a pleasant way to get acquainted. Many members stay after the meeting to have sandwiches and coffee and continue working in the afternoon.

A very happy and successful New Year to you all.

WHY NOT PACK THE POSTPARTUM UTERUS?

(Continued from Page 90)

From our experience, we believe that rather than say, "I have never packed a uterus," it would be better to say, "No uterus has been removed because it was not packed."

Conclusion

A series of 38,403 consecutive deliveries is presented in which 505 uteri were packed because of postpartum hemorrhage due to atony. No hysterectomy was necessary in the 505 packed cases. There was no mortality due to atonic hemorrhage in this series. Our concept of the physiology of postpartum atony is outlined in support of the use of the intrauterine pack.

References

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In Memoriam

RICHARD CHARLES ADAMS

Dr. Richard Charles Adams, a member of the staff of the Mayo Clinic since 1937, died in Worrall Hospital in Rochester, Minnesota, on January 21, 1956. His sudden death was occasioned by a heart attack. He was forty-nine years old.

Dr. Adams was born on August 7, 1906, in Woolner, Ontario, Canada. He attended Queen's University in Kingston, Ontario, from which he received the degrees of Doctor of Medicine and Master in Surgery in 1931. From August, 1931, to January, 1932, he was an intern in the Ottawa General Hospital, Ottawa, Ontario. He then became associated in the practice of general surgery with Dr. J. J. Robertson, of Belleville, Ontario.

Dr. Adams came to Rochester, Minnesota, on October 1, 1935, as a fellow in anesthesiology in the Mayo Foundation, with the accompanying rank of first assistant in anesthesiology. On January 1, 1937, he was appointed to the staff of the Mayo Clinic as a consultant in the Section of Anesthesiology. In 1940, he received the degree of Master of Science in anesthesiology from the University of Minnesota, and in the same year he was appointed an instructor in anesthesiology in the Mayo Foundation, Graduate School, University of Minnesota. He was promoted to assistant professor in 1945, and to associate professor in 1948. From April 1, 1952, to July 1, 1953, Dr. Adams was head of the Section of Anesthesiology at the Mayo Clinic.

When he became a fellow of the Mayo Clinic, Dr. Adams interested himself in the technique of producing anesthesia by the injection of anesthetic agents into veins, a technique known as "intravenous anesthesia." He became widely known for his proficiency in this particular field, and he later carried out investigations on curare.

In 1944, Dr. Adams' book, "Intravenous Anesthesia," was published, and is regarded as an exhaustive work on the subject.

Dr. Adams was certified in 1939 as a specialist in anesthesiology by the American Board of Anesthesiology, Inc. He was a member of the Minnesota State Medical Association, the American Medical Association, the American Society for Pharmacology and Experimental Therapeutics, the Alumni Association of the Mayo Foundation, and the Society of the Sigma Xi. He was a fellow of the American Society of Anesthetists, and served as a member of the board of directors of that organization from 1945 to 1947, and as a member of the House of Delegates in 1948.

Dr. Adams was married to Miss Elma M. Finkle on May 11, 1935. Mrs. Adams and two sons, Richard, eighteen, and Robert, fourteen, survive Dr. Adams.

STEPHEN HENRY BAXTER

Dr. Stephen H. Baxter, seventy-seven, former president of the Hennepin County Medical Society, died December 7, 1955, in Minneapolis. In 1943, Dr. Baxter was president of the Minnesota State Medical Association. He was a member of the "Fifty Club" and had been a life member since 1947.

Dr. Baxter was former director of the Franklin Hospital and senior surgeon at Abbott Hospital for many years. He served on the Board of Public Welfare in Minneapolis and was a past president of the Hennepin County Tuberculosis Association. He was also a member of the board of the Elizabeth Kenny Foundation.

Born in Mechanicsville, Ohio, Dr. Baxter received his medical education at the University of Minnesota. During World War I, he served with the American Expeditionary Forces as a major in the medical corps.

He was a member of Plymouth Congregational Church, the American College of Surgeons, the Minneapolis Surgical Society, and Nu Sigma Nu fraternity.

Dr. Baxter was the nephew of Dr. J. Warren Little who was president of the State Medical Association in 1916.

He is survived by his wife; a son, Stephen H., Jr., Minneapolis; a daughter, Mrs. Benjamin Thurston, Albuquerque, N. M., and a brother, John, Minneapolis.

ROLV SIGVARD HEGGE

Dr. Rolv S. Hegge, physician and surgeon of Austin, died December 17, 1955, after an illness of several years. He was a past president of the Mower County Medical Society.

Born in Austin in 1902, Dr. Hegge attended Austin High School, St. Olaf College, and the medical school of the University of Minnesota. In 1929, he returned to Austin and entered practice with his father, Dr. O. H. Hegge.

Dr. Hegge was Mower County Health Officer for nine years. He was a member of the Westminster Presbyterian Church. He was affiliated with Masonic organizations and a member of the Austin Shrine Club. He was a member of the Minnesota State Medical Association and the American Medical Association.

His survivors include his wife; three daughters, Mrs. Robert Weik of St. Paul, Mrs. Allen Skogebo and Karen Hegge of Austin; his father, and a sister, Mrs. Theodore Heimarck, of Minneapolis.

WILLARD SAMUEL HOWARD

Dr. Willard S. Howard, St. Paul physician, died December 17, 1955, at the age of sixty-six. Born in Rice Lake, Wisconsin, he had been a resident of St. Paul for thirty-five years.

Dr. Howard attended the University of Illinois before serving in the medical corps as a captain during World War I. He was the St. Paul postoffice physician from 1929 to 1946, and then he became associated with the Veterans Administration at Fort Snelling.

He was a member of the Ramsey County Medical Society, the Minnesota State Medical Association and the American Medical Association. He was also a member of the American Legion.

He is survived by two sons, Dr. Robert Howard of Minneapolis, and John, of St. Paul; and a sister, Mrs. Verna Lampman of Austin, Texas.